9

Integrative Summary of Ozone Health Effects

9.1 Introduction

Characterization of the health risks associated with pollutant exposure requires an integrative interpretation of the continuum from air quality to exposure to dose to effects, with full consideration of the actual exposure and susceptibility of different subgroups in the population. The currently published information on population exposure to ozone (O_3) (see Chapter 4) is superseded by recent analyses of the U.S. Environmental Protection Agency (EPA) in a staff paper prepared by the Office of Air Quality Planning and Standards (U.S. Environmental Protection Agency, 1996). Thus, the staff paper contains the risk assessment for O_3.

This chapter characterizes the hazard and dose-response components of risk assessment by integrating the animal toxicological, human clinical and epidemiological, and extrapolation studies of O_3 that were discussed in Chapters 6, 7, and 8, respectively, of this criteria document. Because each of these approaches has different strengths and weaknesses, they were evaluated separately in the respective base chapters; however, a combined evaluation can better describe the full array of effects that are known to occur with exposure to O_3.

The chapter begins with an overview of the relationship between exposure and dose, as this lays a foundation for inter- and intraspecies extrapolation. The chapter then is organized according to biological outcomes, beginning with the effects of short- and long-term exposures of O_3 alone or in ambient air and ending with experimental exposures to binary mixtures with O_3. The section on short-term exposures (i.e., <8 h) presents descriptively symptoms and effects on lung function, exacerbation of existing disease, and cellular-biochemical responses. Quantitative exposure-response relationships for the effects of O_3 on pulmonary function (e.g., changes in lung volume) are summarized separately because the large number of studies allows more complex evaluation and modeling. For the other classes of effects, the more limited exposure-response information is integrated with the description of the effects. The section on long-term exposures encompasses repeated exposures (i.e., 1 to 5 days), prolonged exposures (i.e., months), and genotoxicity and carcinogenicity. Because the available database on binary exposure studies has little predictive value of effects in populations exposed to complex pollutant mixtures, the emphasis is placed on the principles of interaction. The conclusions section is organized according to key questions about the health consequences of O_3 exposure and the population groups that are most likely to be affected.

Because this chapter integrates the results of a large number of studies from the current and earlier O_3 criteria documents (U.S. Environmental Protection Agency, 1978, 1986), it is not practical to provide experimental details or cite specific references. Rather, emphasis is given to main findings that are supported by published, confirmatory studies, unless noted otherwise. Comprehensive details and references are provided in the base chapters (Chapters 6 through 8). A discussion of selective, key references can be found in the summary and conclusion sections of those chapters.

9.2 Exposure-Dose Relationships

Qualitative and quantitative health assessments require, among other things, the ability to relate exposure to dose and dose to effect. In the case of O_3 health assessment, this ability is necessary for two major reasons: (1) to develop unified predictive models of human population responses based on exposure, and (2) to enable extrapolation from animals to humans for chronic effects. Physically and biologically based models of dose simplify the methods of predicting population responses and, in turn, significantly reduce the uncertainty of these predictions. For animal-to-human extrapolations, splitting the problem of exposure and response into an exposure-dose problem and a dose-response problem separates the issue of interspecies sensitivity from purely dosimetric considerations. Responses in animals may be homologous with responses in humans but follow different dose-response curves. By measuring or computing delivered O_3 dose to relevant tissues in animals and humans, transfer functions can, in principle, be developed relating dose-response curves among different species, assuming tissues from different species react in identical fashion. This section discusses the understanding of exposure-dose relationships and how they improve the ability to interpret and predict O_3 responses.

Historically, the first step beyond describing responses solely in terms of exposure concentration was the use of the product of concentration × time × minute ventilation ($C \times T \times \dot{V}_E$), yielding what often has been referred to as an "effective dose". Response modeling has examined the interaction of individual pairs of variables. However, no single model has been able to simply unify any response in terms of the product of $C \times T \times \dot{V}_E$. This is due to the fact that $C \times T \times \dot{V}_E$ is a metric of exposure dose rather than delivered dose and, furthermore, does not account for the mediation of responses in localized regions of the lung that would be responding to local O_3 doses. Advances in O_3 dosimetry modeling and experimental determinations of regional O_3 dose in animals and humans have enabled extensions beyond simple $C \times T \times \dot{V}_E$ modeling to interpret responses.

Ozone dosimetry models provide predictions of the dose distribution of O_3 in the respiratory tract from the trachea to the alveolar spaces of the lung. These models utilize the best available anatomical, physiological, and biochemical data available for animals and humans. These data are incorporated into mathematical formulations of convection, diffusion, and chemical reaction processes in the lung. The models predict that, under resting ventilatory conditions, the O_3 dose per airway generation to all respiratory tract constituents (tissue plus fluid) slowly decreases from the trachea to the terminal and respiratory bronchioles and then declines in the alveolated generations. When dose of O_3 to tissue alone is considered (accounting for reaction and diffusion kinetics in the liquid lining layer), there is a three order of magnitude increase in tissue dose from the trachea to the proximal alveolar regions (PARs), after which the tissue and total dose are virtually equal and fall rapidly in the

alveolated generations. Currently, relationships between delivered regional dose and response are derived assuming that O_3 is the active agent directly responsible for effects; however, there is uncertainty as to the correctness of this assumption. Reactive intermediates, such as peroxides and aldehydes formed when O_3 interacts with constituents of lung lining fluid, may be the agents mediating responses. Thus, the dose of the reactive intermediates may be relevant. Even in the presence of uncertainty over the relevant dose agent, the histopathological findings from chronic O_3 exposures in animals match the predicted distribution of O_3 dose (i.e., the sites of the highest predicted O_3 doses correspond with those regions of the lung with the greatest tissue alterations).

Experimental studies in humans have revealed some important features needed for health assessment. Among these is the observation that the dose of O_3 delivered to the lower respiratory tract is independent of the mode of breathing (i.e., oral versus nasal versus oronasal). This observation simplifies health assessment by eliminating the need for precise information on modes of breathing when considering population responses. Experimental studies in humans also have shown that increasing $\dot{V}_E$ with exercise (increasing both breathing frequency and tidal volume) causes only a small decrease in O_3 uptake efficiency by the total respiratory tract. Based on models of O_3 dose, it appears that the increased $\dot{V}_E$ in exercise, although having little effect on uptake efficiency by the total respiratory tract, causes the distribution of delivered O_3 dose to shift deeper into the respiratory tract. The shift in O_3 dose as a function of $\dot{V}_E$ could help explain the complex relationships seen between response and C, T, and $\dot{V}_E$. An important observation from the human experimental dosimetry studies is the general agreement between O_3 dosimetry models and the measured data.

Experiments in laboratory animals (particularly rats) have been valuable in providing, in conjunction with human experimental data and mathematical dosimetry models, the basis for dosimetric extrapolation. Whereas the human total respiratory tract has an O_3 uptake efficiency between 70 and 100%, the respiratory tract of the rat takes up only about 50% of the inhaled O_3. Unlike the case with humans, the dosimetry models overestimate the uptake efficiency of the rat respiratory tract by approximately 25 to 50% (i.e., the predicted uptake efficiency is between 65 and 75%), but the models are still highly valuable for extrapolation purposes. An important finding has been that the models correctly relate the regional dose of O_3 to the increase in alveolar wall thickness, both of which decline with distance from the junction of the conducting airways and the alveolar regions of the lung.

Experimental O_3 dosimetry and predictive O_3 dosimetry models are informative about the feasibility of extrapolating animal responses to humans. Some acute responses to O_3 can be compared across species on a strict dose-response basis. For example, both animals and humans respond to O_3 in a dose-dependent manner by increasing breathing frequency and decreasing tidal volume (tachypnea). A qualitative comparison between rat and human tachypneic responses at a variety of O_3 concentrations and exercise levels indicates that when exercising, rats and humans have a similar response, but rats are somewhat more responsive at rest. However, when dose to the proximal alveolar region of the lung (normalized to body weight) is considered as the dose metric for tachypneic responses, rats appear to be much more responsive than humans. Another example is influx of protein into the alveolar spaces following O_3 exposure as measured in bronchoalveolar lavage (BAL) fluid. When BAL protein is plotted as a function of pulmonary tissue dose, the rat, guinea pig, rabbit, and human all respond with a similar dose-response pattern, suggesting a common mechanism of response. However, each curve is offset from the other, reflecting overall

sensitivity differences among the species, with the human and guinea pig being more responsive than the rat and rabbit.

Available data on chronic responses to O_3 are considerably more difficult to compare across species. Specific assumptions are required to model exposure-dose relationships. For example, allometric anatomic adjustments provide estimates of unavailable dosimetric data for nonhuman primates, and allometric equivalent life-span estimates better relate the duration of exposure to life-span and cumulative dose. Studies of long-term exposure in monkeys and rats show a near-linear dose-response pattern when alveolar interstitial thickness was related to cumulative dose estimates for the PAR of the lung. Analogous estimates of PAR dose in humans predict similar increases in interstitial thickness at the PAR, with the monkey being more responsive, and the rat less responsive.

9.3 Effects of Short-Term Ozone Exposures

9.3.1 Physiological Responses to Ozone Exposure

Typical acute physiological responses to O_3 exposure observed in both human clinical and field studies include a reduction in forced vital capacity (FVC), decreased expiratory flow rates, and increased respiratory symptoms. The most common symptoms include cough, airway irritation, and chest discomfort associated with deep inhalation. These responses are often accompanied by increased airway resistance and tachypnea. The voluntary spirometry and symptom responses cannot be elicited from animals, but their tachypneic response is well documented. Ozone exposure also increases airway responsiveness to nonallergenic airway stimuli (e.g., histamine) in humans and animals. There is a large range of physiological responses among humans, with at least a 10-fold difference between the most and least responsive individuals.

9.3.1.1 Respiratory Symptom Responses

An association between O_3 exposure and the presence of symptoms has been shown in human clinical, field, and epidemiological studies. Prevalent symptoms include cough, irritation of the airways (described as a scratchy throat or discomfort under the sternum), and discomfort when taking a deep breath (described as chest tightness or pain in the chest). Eye irritation, sometimes reported as a symptom in field or epidemiological studies with exposure to oxidant mixtures including peroxyacyl nitrates, is not associated with exposure to O_3 alone. The most prevalent respiratory symptoms have a much higher incidence in young adults than in older adults and generally are not reported in children or adolescents. Asthmatics have symptoms similar to nonasthmatics but also report a higher incidence of wheezing. The receptors responsible for cough may be unmyelinated C-fibers or rapidly adapting receptors located in the larynx and the largest conducting airways. Thus, there appears to be a potential mechanistic linkage between coughing and changes in spirometry. Field and epidemiological studies also indicate an association between hourly or daily ambient O_3 levels and the presence of respiratory symptoms, particularly cough. Such associations may be most evident in asthmatic children. Although symptoms cannot be elicited from animals, indirect measures of symptom responses in animals include behavioral responses (e.g., decreased wheel-running activity, decreased activity associated with obtaining food) indicative of aversion to O_3 exposure.

Symptom responses to O_3 exposure follow a monotonic exposure-response relationship that has a similar form to that for spirometry responses. Increasing exposure levels elicit increasingly more severe symptoms that persist for longer periods. Symptom and spirometry responses follow a similar time course during an acute exposure and the subsequent recovery, as well as over the course of several days in a repeated exposure study. Furthermore, medication interventions that block or reduce spirometry responses have a similar effect on symptom responses. Levels at which symptoms occur under various exposure conditions are discussed in Section 9.3.4.2. As with spirometry responses, symptom responses vary considerably among subjects, although the individual correlations between spirometry and symptom responses are relatively low. Ozone induces interference with exercise performance, either by reducing maximal sustainable levels of activity or by reducing the duration of activity that can be tolerated at a particular work level; this is likely related to symptoms. In several heavy or severe exercise studies of athletes exposed to O_3, the discomfort associated with the respiratory symptoms caused by O_3 concentrations in excess of 0.18 ppm was of sufficient severity that the athletes reported that they would have been unable to perform maximally if the conditions of the exposure were present during athletic competition. In workers or active people exposed to ambient O_3, respiratory symptoms may cause reduced productivity or may curb the desire to pursue certain leisure activities.

9.3.1.2 Lung Function Responses

Epidemiological, field, and chamber studies have demonstrated that acute exposure to O_3 decreases FVC and forced expiratory volume in 1 s (FEV_1). In humans, O_3 exposure reduces FVC primarily by decreasing inspiratory capacity. This is believed to be the result of neurogenic inhibition of maximal inspiration, possibly caused by stimulation of C-fiber afferents, either directly or from O_3-induced products of inflammation. C-fibers are also thought to be the receptors responsible for the cough reflex in humans. After exposure to O_3, coughing frequently is elicited during the deep inspiration prior to the forced expiratory maneuver used in dynamic spirometry tests such as FVC, FEV_1, and forced expiratory flow at 25 to 75% of FVC. The observation that nonsteroidal anti-inflammatory drugs (e.g., indomethacin, ibuprofen) reduce or block spirometric responses to O_3 exposure and reduce levels of prostaglandin E_2 (PGE_2) within the lung suggests that mediators released by damaged epithelial cells and alveolar macrophages may play a role in the inhibition of maximal inspiration. Although it seems clear that the reduction in total lung capacity is not attributable to reduced static compliance (i.e., a stiffer lung) or inspiratory muscle weakness, other mechanisms may be involved. Increased interstitial fluid in patients with heart disease causes a decrease in vital capacity and frequency-dependent decreases in lung compliance. The O_3-induced tachypneic response, seen in many animal species and in exercising humans, may be related to the decrease in vital capacity. In humans, the pulmonary reflexes that inhibit maximal inspiration may also limit tidal volume during exercise, which leads to a compensatory tachypnea. The tachypneic response in humans may not be entirely involuntary because it has been reported that O_3-exposed subjects may consciously modify their breathing pattern to relieve discomfort.

The time course of the spirometry responses to O_3 exposure depends on the exposure conditions. At low levels of exposure (e.g., light exercise and O_3 concentration <0.18 ppm), responses are induced slowly and progressively and they may or may not reach a plateau of response, depending on the duration of the exposure. At higher levels of exposure (e.g., very heavy exercise and O_3 concentration >0.25 ppm), responses occur rapidly (within

15 min), and the largest portion of the response tends to occur early in exposure, indicative of a plateau of response that typically is not achieved because of termination of the exposure within 1 to 2 h. The quantitative exposure-response relationships are discussed more extensively in Section 9.3.4.

In both chamber and field studies, the responses of healthy children to acute O_3 exposure are similar to those seen in adults. Responses of children and adolescents exposed to ambient O_3 (and other copollutants) at summer camps in at least six different locations in the northeastern United States, southeastern Canada, and Southern California indicate changes in spirometry similar to those found in individuals exposed to O_3 under controlled experimental conditions. There is a substantial range of response among individuals in camp studies and between various locations; however, the average FEV_1 was lower when ambient O_3 was higher. Although direct comparisons cannot be made because of incompatible differences in experimental design and analytical approach, this range of response is comparable to the range of response seen in chamber studies at low O_3 concentrations. In the "camp studies", a key measurement is the slope of the relationship between FEV_1 and the measured O_3 concentration during the previous hour, without consideration of the background O_3 levels (even though exposures occurred over multiple hours). The average slope from six studies was −0.50 mL/ppb within an O_3 concentration range of 0.01 to 0.16 ppm (see Chapter 7). For an exposure to 0.12 ppm O_3, this corresponds to a decrease in FEV_1 of 60 mL from a base level of approximately 2,000 to 2,500 mL, or a 2.4 to 3.0% decrease in FEV_1. This is comparable to the findings of McDonnell et al. (1985) for 8- to 11-year-old boys who experienced a 3.4% decrease in FEV_1 after being exposed to 0.12 ppm O_3 for 2 h. Recent studies in adults performing outdoor exercise also have shown an association between decreased spirometric responses and increased ambient O_3 levels.

A consistent finding across many animal species is that O_3 causes rapid shallow breathing (O_3-induced tachypnea), which, in humans, may be related to a sensation of discomfort associated with taking large tidal breaths. Of particular interest for comparing interspecies responses is that the responses of rats and guinea pigs fall within the same range as seen for humans from rest to heavy exercise.

Common pulmonary function tests do not measure changes in the small airways of the centriacinar region of the lung (that segment between the last conducting airway and the gas exchange region), which is highly susceptible to damage by O_3 and is the site of epithelial cell necrosis and remodeling of respiratory bronchioles. Numerous pulmonary function tests reputed to measure responses in small airways (e.g., closing volume, aerosol bolus) have been used in O_3 studies. Responses have been demonstrated, but it is not clear that these tests correlate with the morphological lesion observed in the small airways of experimental animals (see Section 9.4), which is predicted to occur in humans but has not been confirmed reliably through comparable morphologic data from humans residing in O_3-polluted areas. Even if small airways disease is demonstrated in humans, there is as yet no compelling evidence that it will progress to chronic lung disease.

An increase in airway resistance is an indication of the response of large airways to O_3 exposure and is mechanistically different from lung volume responses. Also, higher O_3 concentrations are required to change airway resistance compared to FEV_1. Changes in specific airway resistance (SR_{aw}) of healthy subjects following O_3 exposure are small relative to those seen in asthmatics with an inhalation exposure to a bronchoconstricting drug (methacholine), a specific antigen, or sulfur dioxide (SO_2). In rats exposed to O_3, changes in

resistance also tend to be small. The observation that changes in airway resistance are modest clearly indicates that reductions in maximum expiratory flow are not caused primarily by narrowing of large airways. The increase in airway resistance appears to be vagally mediated because it is sensitive to inhibition by atropine.

9.3.1.3 Changes in Airway Responsiveness

Ozone exposure also causes increased responsiveness of the pulmonary airways to subsequent challenge with bronchoconstrictor drugs such as histamine or methacholine. This phenomenon is seen even after recovery from spirometric changes, but it typically is no longer present after 24 h. Although changes in airway responsiveness tend to resolve somewhat more slowly and appear to be less likely to be attenuated with repeated exposure, the evidence for a persistent increase in responsiveness from animal studies is inconsistent. Changes in airway responsiveness in rats and guinea pigs tend to occur at higher O_3 concentrations and, as in humans, tend to be most pronounced shortly after the exposure and less so 24 h postexposure. Changes in airway responsiveness appear to occur independently of changes in pulmonary function. This response may not be due to the presence of polymorphonuclear leukocytes (PMNs) in the airway or to the release of arachidonic acid metabolites, but could possibly be due to epithelial damage and the consequent increased access of these chemicals to smooth muscle in the airways or to the receptors in the airways responsible for reflex bronchoconstriction. The clinical relevance of this observation is that, after O_3 exposure, human airways may be more susceptible to a variety of stimuli, including antigens, chemicals, and particles. One animal study has demonstrated decreased antigen-induced bronchoconstriction after O_3 exposure, and a human study in allergic asthmatics is suggestive of an increase in such a response. An increased response to inhalation of a specific antigen to which a human is sensitized is a plausible outcome of O_3 exposure. However, ongoing studies of this phenomenon will need to be evaluated in order to determine the exposure-response relationship for alterations in responses to inhaled antigens, especially with regard to sensitive asthmatics. Enhanced response to antigens in asthmatics could lead to increased morbidity (i.e., medical treatment, emergency room visits, hospital admissions) or to more persistent alterations in airway responsiveness.

9.3.2 Exacerbation of Respiratory Disease

People with preexisting pulmonary disease may be at increased risk from O_3 exposure. Because of their existing functional limitations, any further decrease in function would lead to a greater overall functional decline. Furthermore, some individuals with pulmonary disease may have an inherently greater sensitivity to O_3. Asthmatics, by definition, have inherently greater bronchial responsiveness, but, depending on the severity of their disease and its clinical status, their FEV_1 can be within the normal range (100 ± 20% predicted) or may be less than 50% predicted. Patients with chronic obstructive pulmonary disease (COPD) can have FEVs ranging from 30 to 80% of predicted, again depending on disease severity. Because of their depressed functional state, small absolute changes in lung function have a larger relative impact. For example, a 500-mL FEV_1 decrease in a healthy young man with an FEV_1 of 4,000 mL causes only a 12% decline. In a 55-year-old COPD patient with an FEV_1 that is 50% of predicted, or about 1,670 mL, a 500-mL decline in FEV_1 would result in a 30% decline in FEV_1. Asthmatics with depressed baseline function would have similarly magnified relative responses and, because of increased bronchial

responsiveness, may also experience larger changes in airway resistance. Evaluating the intersection of risk factors and exposures is more complex. For example, an individual with more severe lung disease is unable to exercise heavily and thus would be less likely to encounter an effective exposure.

About 10 million people in the United States (4% of the population) are estimated to have asthma (National Institutes of Health, 1991). The prevalence is higher among African Americans, older (8- to 11-year-old) children, and urban residents (Schwartz et al., 1990). Death due to asthma is an infrequent event; on an annual basis, about one death occurs per 10,000 asthmatic individuals. Mortality rates are higher among males and are at least 100% higher among nonwhites. In two large urban centers (New York and Chicago), mortality rates from asthma among nonwhites may exceed the city average by up to fivefold (Sly, 1988; Evans et al., 1987; National Institutes of Health, 1991; Weiss and Wagener, 1990; Carr et al., 1992). Although some innercity areas may have lower O_3 concentrations than some suburban areas, the concentrations are much higher than those in most rural areas. The impact of ambient O_3 on asthma morbidity and mortality in this apparently susceptible population is not well understood. The few epidemiological studies are subject to confounding factors and have rarely focused on innercity nonwhite asthmatics. Furthermore, controlled human exposure studies of asthmatics typically include mild to moderate asthmatics and have not dealt specifically with nonwhite asthmatics.

A number of epidemiological studies have shown a consistent relationship between ambient oxidant exposure and acute respiratory morbidity in the population. Small decreases in forced expiratory volumes and increased respiratory symptoms, including exacerbation of asthma, occur with increasing ambient O_3, especially in children. Modifying factors, such as ambient temperature, aeroallergens, and other copollutants (e.g., particles) also can contribute to this relationship. Ozone air pollution can account for a portion of summertime hospital admissions and emergency department visits for respiratory causes; studies conducted in various locations in the eastern United States and Canada consistently have shown a relationship with increased incidence of visits and admissions, even after controlling for modifying factors, as well as when considering only concentrations <0.12 ppm O_3. It has been estimated from these studies that O_3 may account for roughly one to three excess summertime respiratory hospital admissions per hundred parts per billion O_3, per million persons.

The association between elevated ambient O_3 concentrations during the summer months and increased hospital visits and admissions has a plausible biologic basis in the physiologic, symptomatic, and field study evidence discussed earlier. Specifically, increased airway resistance, airway permeability, and incidence of asthma attacks and airway inflammation suggest that ambient O_3 exposure could be a cause of the increased hospital admissions, particularly for asthmatics.

The associations found in the epidemiological studies are supported by chamber studies. Asthmatics and nonasthmatics have qualitatively similar responses to chamber O_3 exposures. Although symptom and volume-related responses (i.e., decreased FVC) tend to be similar, airway resistance increases relatively more, from an already higher baseline, in asthmatics exposed to O_3. Ozone-induced alterations in responsiveness to bronchoconstrictor drugs show similar changes in asthmatics and nonasthmatics. There is no evidence at this time that O_3 induces a persistent increase in airway responsiveness or that O_3-exposed asthmatics are more likely to have a late-phase response to specific antigen challenge. Symptom responses also have been reported in asthmatics exposed to O_3. In contrast to

nonasthmatics, wheezing, a typical finding in asthma, is a prevalent symptom in addition to the cough, chest tightness, and shortness of breath that are reported by subjects without asthma.

9.3.3 Morphological and Biochemical Abnormalities

9.3.3.1 Inflammation and Cell Damage

Ozone-induced cell injury may lead to effects including inflammation, altered permeability of the epithelial barrier, impaired host defense and particle clearance, irreversible structural alterations in the lung, exacerbation of preexisting disease (e.g., asthma), and increased sensitivity to biocontaminants (e.g., allergens). Of these, O_3-induced inflammation of the respiratory tract has been best documented and occurs in all species that have been studied. The mechanisms leading to the observed inflammatory responses induced by O_3 are just beginning to be understood. Both animal morphological studies and in vitro studies indicate that airway ciliated epithelial cells and Type 1 cells are the most O_3-sensitive cells and are initial targets of O_3. These cells are damaged by O_3 and produce a number of proinflammatory mediators (e.g., interleukins [IL-6, IL-8], PGE_2) capable of initiating a cascade of events leading to PMN influx into the lung, activation of alveolar macrophages, inflammation, and increased permeability across the epithelial barrier.

Ozone-Induced Inflammation

Ozone causes inflammatory changes throughout the respiratory tract, including the nose. Humans and laboratory animals exposed to O_3 develop inflammation and increased permeability in the nasal passages. A recent study reported a positive correlation between nasal inflammation in children and measured ambient O_3 concentrations. Studies with rats suggest a potential competing mechanism between the nose and lung, with inflammation occurring preferentially in the nose at low O_3 concentrations and shifting to the lung at higher concentrations. It is unclear if this represents a specialization restricted to rats or is a more general phenomenon.

In general, inflammation can be considered as the host response to injury and the induction of inflammation as evidence that injury has occurred. Inflammation induced by exposure of humans to O_3 can have several potential outcomes: (1) inflammation induced by a single exposure (or several exposures over the course of a summer) can resolve entirely; (2) continued acute inflammation can evolve into a chronic inflammatory state; (3) continued inflammation can alter the structure and function of other pulmonary tissue, leading to diseases such as fibrosis; (4) inflammation can alter the body's host defense response to inhaled microorganisms, particularly in potentially vulnerable populations such as the very young and old; and (5) inflammation can alter the lung's response to other agents such as allergens or toxins. Except for outcome (1), the possible chronic responses have not been identified with inflammation induced by exposure of humans to O_3. It is also possible that the profile of response can be altered in persons with preexisting pulmonary disease (e.g., asthma, COPD) or smokers.

The recent use of BAL as a research tool in humans has afforded the opportunity to sample cells and fluid from the lung and lower airways of humans exposed to O_3 and to ascertain the extent and course of inflammation and its constitutive elements. Several studies have shown that humans exposed acutely (1 to 3 h) to 0.2 to 0.6 ppm O_3 had O_3-induced inflammation, cell damage, and altered permeability of epithelial cells lining the respiratory

tract (allowing components from plasma to enter the lung). For individuals acutely exposed to 0.4 to 0.6 ppm O_3, PMNs (the hallmark cells of inflammation) make up 8 to 10% of the recovered BAL cells. This represents a five- to eightfold increase in PMNs compared with similar individuals exposed to clean air, who typically have 1 to 2% PMNs in their BAL fluid. The lowest concentration of O_3 tested, 0.08 ppm for 6.6 h with moderate exercise, also induced small but statistically significant increases in a number of inflammatory mediators, including PMNs.

The percent of PMNs in BAL fluid taken from individuals exposed to 0.4 ppm O_3 for 2 h equals or exceeds those found in individuals exposed to other environmental toxicants, such as asbestos or silica, or in individuals with idiopathic pulmonary fibrosis (IPF) or connective tissue disorders (CTD) (Cherniak et al., 1990). For example, individuals with a history of occupational exposure to asbestos (>10 years) have 3.3 ± 1.3% BAL PMNs, and individuals with a history of occupational exposure to silica (>2 years) have 1.4 ± 0.4% PMNs. Untreated patients newly diagnosed with IPF have 6.7 ± 2.5% PMNs, whereas those with CTD have 16 ± 11.6% PMNs. Baseline levels of PMNs in patients with asthma do not differ significantly from healthy individuals, although PMN levels can increase following allergen bronchoprovocation (Smith and Deshazo, 1993). In contrast, PMNs can make up as much as 80% of BAL cells in patients with acute bacterial infections (Stanley, 1991).

Short-term (<8 h) exposure of animals to O_3 also results in cell damage, inflammation, and altered permeability, although, in general, higher O_3 concentrations are required to elicit a response equivalent to that of humans. Because humans were exposed to O_3 while exercising and most animal studies were done at rest, differences in ventilation likely play a significant role in the different response of humans and rodents to the same O_3 concentration. Studies in which animals were exposed at night (during their active period) or in which ventilation was increased with CO_2 tend to support this idea.

Studies utilizing BAL techniques sample only free or loosely adherent cells in the lung; thus, it is possible that cellular changes have occurred in the interstitium that are not reflected in BAL studies, or that BAL changes exist in the absence of interstitial changes. However, morphometric analyses of inflammatory cells present in lung and airway tissue sections of animals exposed to O_3 are in general agreement with BAL studies. Short-term O_3 exposure (<8 h) causes similar types of alterations in lung morphology in all laboratory animal species studied. The most affected cells are the ciliated epithelial cells of the airways and Type 1 cells in the alveolar region. The centriacinar region (the junction of the conducting airways and gas exchange region) is a primary target, possibly because it receives the greatest dose of O_3 delivered to the lower respiratory tract. Sloughing of ciliated epithelial and Type 1 cells occurs within 2 to 4 h of exposure of rats to 0.5 ppm O_3.

Time Course of Ozone-Induced Inflammatory Response

Findings from human and animal studies agree that the O_3-induced inflammatory response occurs rapidly and persists for at least 24 h. Increased levels of PMNs and protein are observed in the BAL fluid within 1 h following a 2-h exposure of humans to O_3 and continue for at least 20 h. The kinetics of response during this time have not been well studied in humans, although a single study shows that PMN levels are higher at 6 h postexposure than at 1 or 20 h in different individuals. Several animal studies suggest that BAL PMN and protein levels peak 12 to 16 h after an acute O_3 exposure and begin to decline by 24 h, although some studies report detectable BAL PMNs even 36 h after exposure. It is also clear that in humans the pattern of response differs for different

inflammatory mediators. Mediators of acute inflammation, such as IL-6 and PGE_2, are more elevated immediately after exposure; whereas mediators that potentially could play a role in resolving inflammation, such as fibronectin and plasminogen activator, are preferentially elevated 18 h after exposure. The rapidity with which cellular and biochemical mediators are induced by O_3 makes it conceivable that some of them may play a role in O_3-induced changes in lung function—indeed there is some evidence that BAL PGE_2 levels are correlated with decrements in FEV_1, and anti-inflammatory medications that block PGE_2 production also reduce or block the spirometric responses to O_3. Although earlier studies suggested that O_3-induced PMN influx might contribute to the observed increase in airway hyperreactivity, animal studies show that when PMNs are prevented from entering the lung, O_3-induced hyperreactivity or increases in many inflammatory mediators still occur. In addition, studies in which anti-inflammatory drugs are used to block O_3-induced lung function decrements still show increases in PMNs and most other inflammatory mediators (although PGE_2 is not increased).

Individuals and Populations Susceptible to Ozone

To date, there have been no studies that have examined the cellular/biochemical response to O_3 of potentially susceptible subpopulations, such as asthmatics, nor are there any data in humans addressing whether age, gender, or racial differences can modify the inflammatory response to O_3. Increased susceptibility of asthmatics or chronic bronchitics could be hypothesized on the basis that they have an underlying inflammatory disease that may be exacerbated with an otherwise small magnitude of change. Inflammation is not induced to the same extent in all individuals. In moderately exercising humans exposed to 0.08 ppm O_3 for 6.6 h, the mean changes in inflammatory indices were low, but some individuals had increases comparable to those reported in heavily exercising subjects exposed to 0.4 ppm O_3 for 2 h, suggesting that some segments of the population may be more responsive to low levels of O_3. It has not yet been studied whether intersubject differences in inflammatory response to O_3 are reproducible over time for the same subject, as has been shown for intersubject differences in lung function. There seems to be no strong correlation between the various mediators of inflammation, cell damage, and permeability (i.e., those individuals with the greatest PMN response are not necessarily those with the greatest BAL protein, PGE_2, or IL-6 response). Furthermore, the magnitude of lung function decrements and respiratory symptoms has not yet been shown to be correlated with mediators of inflammation, with the possible exception of PGE_2.

Animal studies also show large interspecies and interstrain differences in response to O_3 and suggest that genetic factors may play a role in susceptibility to O_3. Different rat strains respond to O_3 differently; for example, Wistar rats have the greatest PMN influx, whereas Fischer rats demonstrate the most epithelial cell damage. In addition, limited data suggest that dietary antioxidant levels may affect the response of rodents to O_3 and that very young rats produce more PGE_2 in response to O_3 than do older rats. Taken as a whole, the human and animal studies suggest that the inflammatory response to O_3 is complex and that determinants of susceptibility may occur at several different genetic loci.

9.3.3.2 Host Defense

The mammalian respiratory tract has a number of closely integrated defense mechanisms that, when functioning normally, provide protection from the adverse effects of a wide variety of inhaled particles and microbes. Impaired mucociliary clearance can result in unwanted accumulation of cellular secretions and increased numbers of particles and microorganisms in the lung, leading to increased infections and bronchitis.

Mucociliary Clearance of Inhaled Particles

Animal studies show that clearance of inhaled insoluble particles is slowed after acute exposure to O_3. Ozone-induced damage to cilia and increased mucus secretion likely contribute to a slowing of mucociliary transport rates. Interestingly, retarded mucociliary clearance is not observed in animals exposed repeatedly to O_3. The effects of O_3 on mucociliary clearance in humans have not been well studied, and the results are somewhat conflicting; one study reports an O_3-induced increase in particle clearance in subjects exposed to 0.4 ppm O_3 for 2 h, and another study reports no O_3-induced change in particle clearance with a similar exposure regimen.

Alveolar Macrophage Function

Macrophages represent the first line of defense against inhaled microorganisms and particles that reach the lower airways and alveoli. Studies in both humans and animals have shown that there is an immediate decrease in the number of BAL macrophages following O_3 exposure. Alveolar macrophages also have been shown to be crucial to the clearance of certain gram-positive bacteria from the lung. Several studies in both humans and laboratory animals also have shown that O_3 impairs the phagocytic capacity of alveolar macrophages, and some studies suggest that mice may be more impaired than rats. The production of superoxide anion (an oxygen radical used in bacterial killing) by alveolar macrophages also is depressed in both humans and animals exposed to O_3, and the ability of alveolar macrophages to kill bacteria directly is impaired. Decrements in alveolar macrophage function have been observed in moderately exercising humans exposed to the lowest concentration tested, 0.08 ppm O_3 for 6.6 h.

Interaction with Infectious Agents

Concern about the effect of O_3 on susceptibility to respiratory infection derives primarily from animal studies in which O_3-exposed mice die following a subsequent challenge with aerosolized bacteria. Increased mortality of experimental laboratory animals has been shown to be concentration-dependent, and exposure to as little as 0.08 ppm O_3 for 3 h can increase mortality of mice to a subsequent challenge with streptococcus bacteria. In addition, younger mice are more susceptible to infection than older mice; this has been related to increased PGE_2 production in these animals, which likely decreases alveolar macrophage activity.

It has been suggested that impaired alveolar macrophage function is the mechanism likely responsible for enhanced susceptibility to bacteria. However, mortality is not observed with other rodent species, raising the question of whether this phenomenon is restricted to mice. Although both mice and rats show impaired macrophage killing of inhaled bacteria following O_3 exposure, rats mount a faster PMN response to O_3 to compensate for the deficit in alveolar macrophage function. The slower clearance time in mice allows the streptococcus strain to persist in lung tissue and, subsequently, to elaborate a number of virulence factors

that evade secondary host defense and lead to bacterial multiplication and death of the host. Although increased mortality in laboratory animals is not directly relevant to humans, laboratory animals and humans share many host defense mechanisms being measured by mortality in the mouse model. Thus, the category of effect (i.e., decrement in antibacterial defenses) can be qualitatively extrapolated to humans.

There is no compelling evidence from animal toxicological, human clinical, or epidemiological studies that O_3 increases the incidence of respiratory viral infection in humans. A study of experimental rhinovirus infection in susceptible volunteers failed to show any effect of 5 consecutive days of O_3 exposure (0.3 ppm, 8 h/day) on the clinical picture or on host response. Studies in which O_3-exposed mice were challenged with influenza virus have conflicting results: some studies show increased mortality, some show decreased mortality, and still others show no change at all. However, even when increased mortality was demonstrated, there was no difference in viral titers in the lung, suggesting virus-specific immune functions were not altered. One animal study found that, although subchronic O_3 exposure did not affect the acute course of a viral infection, it did enhance postinfluenzal alveolitis.

Taken as a whole, the data clearly indicate that an acute O_3 exposure impairs the host defense capability of both humans and animals, primarily by depressing alveolar macrophage function and perhaps also by decreasing mucociliary clearance of inhaled particles and microorganisms. This suggests that humans exposed to O_3 could be predisposed to bacterial infections in the lower respiratory tract. The seriousness of such infections may depend on how quickly bacteria develop virulence factors and how rapidly PMNs are mobilized to compensate for the deficit in alveolar macrophage function.

Ozone also has been reported to suppress natural killer cell activity in the lung, to suppress proliferative responses to bacterial antigen (Listeria) in both spleen and bronchial lymph nodes, and to induce delayed hypersensitivity responses to Listeria antigen. However, these effects occur at higher exposure levels (0.75 to 1.0 ppm O_3) than those that affect macrophage function.

9.3.4 Quantitative Ozone Exposure-Response Relationships

A quantitative understanding of the relationship between O_3 exposure and subsequent response is useful both for a better understanding of the processes underlying outcomes of interest and for purposes of prediction. Examples of the utility of the latter include identification of exposures unlikely to produce effects, risk and benefits assessment, and prediction of responses based on exposures for which empirical data do not exist. In general, exposure-response relationships have been better characterized for populations than for individuals, and, although the form of the relationships may differ, those for individuals are likely to be qualitatively similar to those of populations. On the other hand, because of large differences in responsiveness among individuals, exposure-response relationships for the population may not reflect quantitatively the experience of a given individual.

Relationships between short-term exposure and acute response have been described for lung function changes, induction of symptoms, and BAL outcomes in experimental exposure studies and for lung function, symptoms, hospital and emergency room admissions, and mortality in epidemiologic studies. Exposure in the experimental studies can be defined in terms of concentration, dose rate of exposure, total inhaled dose, and dose at the active site. The limiting factor in modeling exposure-response with experimental data has been that

no single study has included a wide enough range of the three exposure variables of interest (i.e., C, $\dot{V}_E$, T) to choose between models or to identify the appropriate method of describing exposure.

Exposure-response models in the epidemiologic studies generally have included only O_3 concentration measured at a central monitoring site in the study area as the exposure variable. With some exceptions, characterization of exposure-response relationships in these studies has been limited by little information on activity level or duration of exposure, a generally narrow range of exposure concentrations, the need for complex models to control for potential confounding by other pollutants and extraneous variables, and outcomes for which only a small fraction of the variance is explained by exposure to pollutants. These factors make selection among various models of response difficult.

A number of exposure-response functions have been proposed to describe the results of experimental studies. No single exposure-response model form, however, has been adequately tested and identified as providing an accurate, precise description of the relationship between exposure and response in both humans and laboratory animals for lung function or BAL endpoints. Rather, for a given study, a particular model may have been selected a priori to describe the exposure-response data or may have been identified as providing the best fit among several competing models. In many cases, models have been found to be deficient, but rarely has the performance of a number of possible models been systematically compared.

From the individual studies, several important observations have been made that are qualitatively true for describing BAL and pulmonary function responses in both humans and laboratory animals and that should be considered in the selection of a model to describe population response as a function of exposure. Response increases monotonically with C, $\dot{V}_E$, and T, with C generally being a stronger predictor of response than $\dot{V}_E$ or T. The relationship between response and one of the exposure variables is dependent on the level of the other two variables. The relationship between response and each of the exposure variables is curvilinear over a wide range of exposure conditions, although it may appear linear over certain narrow ranges of exposure. With increasing duration of response (and possibly with increasing concentration), the FEV_1 response may approach a plateau in humans. Some evidence exists suggesting that the level of the plateau with T is a function of C. This plateau has not been observed in animal studies or for BAL endpoints. Respiratory symptom responses generally follow a pattern similar to that observed for spirometry (e.g., mean responses increase with increasing C, $\dot{V}_E$, and T). As with spirometry responses, large individual differences in symptom responses occur. Little analytical work, however, has been performed that mathematically describes either the mean or individual responses as multivariable functions of C, $\dot{V}_E$, and T.

Exposure-response models of FEV_1 and BAL responses in laboratory animals that have been proposed and that fit to varying degrees include linear and polynomial models of C, $\dot{V}_E$, and T, with and without cross-product terms (e.g., C × T); exponential models utilizing C × T as the exposure variable at constant $\dot{V}_E$; and cumulative normal probability or logistic models utilizing C^y × T as the exposure variable at constant $\dot{V}_E$. Models of these types have been found under some circumstances to describe the relationship between exposure and response for a particular data set. Most single data sets, however, do not include a wide enough range of data to test adequately the performance of a particular model across a wide range of exposure conditions or to identify an appropriate exposure metric. In particular, recent efforts have focused on the relationship between response and C and T at

constant $\dot{V}_E$. No definitive work has addressed the modeling of response and $\dot{V}_E$ for a given endpoint or for consideration of $\dot{V}_E$ changing as a function of T. Because animal and human studies often are conducted at different relative levels of $\dot{V}_E$, and because techniques to adjust mathematically for these differences only now are being developed, efforts to compare responses across species or to develop extrapolation models have been hampered. As noted earlier, quantitative models currently do not exist for respiratory symptoms.

Evidence indicates that, for humans and animals, the exposure-response relationship of BAL and pulmonary function outcomes may be modified by previous recent exposure to O_3, and the relationship for FEV_1 changes in humans may be modified by age. Previous exposure to O_3 has not been included in any exposure-response models. For young adults, the modification of the exposure-response relationship by age has been modeled.

Exposure-response models of lung function in epidemiologic studies generally have been limited to linear models of response as functions of various O_3 exposure metrics (e.g., 1-h or 8-h daily maximum, etc.). A number of studies have demonstrated significant negative mean linear relationships between O_3 exposure and lung function. Exposure-response models of respiratory symptoms in epidemiologic studies generally have employed logistic regression techniques with O_3 or total oxidant concentration as the exposure variable. These latter models generally have been chosen a priori reflecting the categorical nature of the outcome variable rather than by comparison of the performance of several candidates.

Ecological studies of the relationship between daily rates of emergency room or hospital admissions or mortality and O_3 exposure have utilized a variety of complex exposure-response models with some metric of daily O_3 concentration as the exposure variable. The complexity of the models results from, among other things, the need to control for potentially confounding long-wave patterns in the health outcomes in relationship to other potential confounders, such as other air pollutants, seasonal and meteorological factors, holidays, and day-of-week effects. In various studies, both linear and nonlinear functions have been used to describe the relationship between adjusted health outcome and concentration.

In summary, O_3 is no exception to the general problems encountered in all studies of environmental epidemiology. No single universal model form has been identified that accurately and precisely describes the relationship between population exposure and response under all circumstances. In general, the ability of a predictive model based on one study to predict responses from an independent study has not been studied adequately. For purposes of prediction or risk estimation, the adequacy of fit of a given model in a given data set and the size and representativeness of the sample should be assessed. Extrapolation beyond the range of observed data introduces additional uncertainty into predictions or risk estimates.

9.3.4.1 Prediction and Summary of Mean Responses

A selection of published reports in which models of population or mean responses have been developed is listed below, along with figures summarizing examples of predicted quantitative exposure-response relationships. Reports numbered 5 and 11 are epidemiological studies, and the remainder are experimental studies. Because no currently available single model is sufficient to accurately describe all major scenarios, the key models are presented without weighting. Following this section is a further section that describes models of individual responses within the population.

1. Hazucha (1987) predicts mean FEV_1 decrements in humans as a function of C (0.0 to 0.75 ppm O_3) for four levels of $\dot{V}_E$ for 2-h exposures (Figure 9-1).

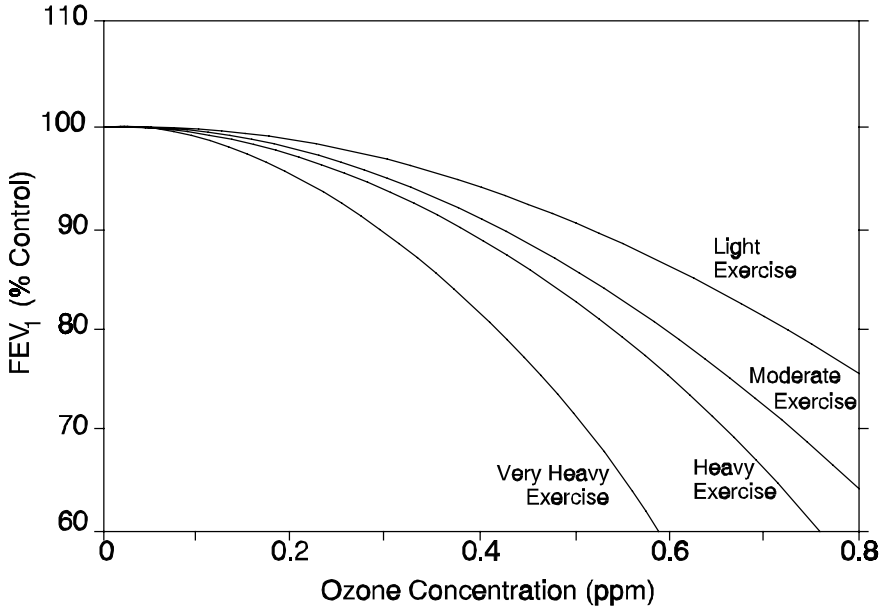

Figure 9-1. Mean predicted changes in forced expiratory volume in 1 s following 2-h exposures to ozone with increasing levels of intermittent exercise.

Source: Hazucha (1987).

2. McDonnell and Smith (1994) predict mean FEV_1 decrements in heavily exercising humans as a function of C (0.0 to 0.4 ppm O_3) and T (1.0 to 6.6 h) (Figure 9-2).
3. Highfill et al. (1992) predict the BAL responses of resting rats and guinea pigs as a function of C (0.0 to 0.8 ppm O_3) and T (2 to 8 h) (Figure 9-3).
4. Tepper et al. (1994) predict the FVC changes as a function of C (0.0 to 0.8 ppm O_3) and T (2 to 7 h) for exposures conducted with rats breathing at three times resting $\dot{V}_E$ (Figure 9-4).
5. Burnett et al. (1994) predict the frequency of hospital admissions (adjusted for covariates) as a linear function of C (previous day 1-h O_3 maximum) for Ontario hospitals (Figure 9-5).

Other reports in which models are developed or that contain data potentially useful for further development or testing of models are listed below.

6. Seal et al. (1993) present data that would allow modeling of FEV_1 decrements in humans as a function of C (0.0 to 0.4 ppm O_3) for 2-h exposures with moderate exercise.
7. Folinsbee et al. (1978) predict lung function changes in humans as a function of C (0.0 to 0.50 ppm O_3) and $\dot{V}_E$ (10 to 65 L/min) for 2-h exposures.

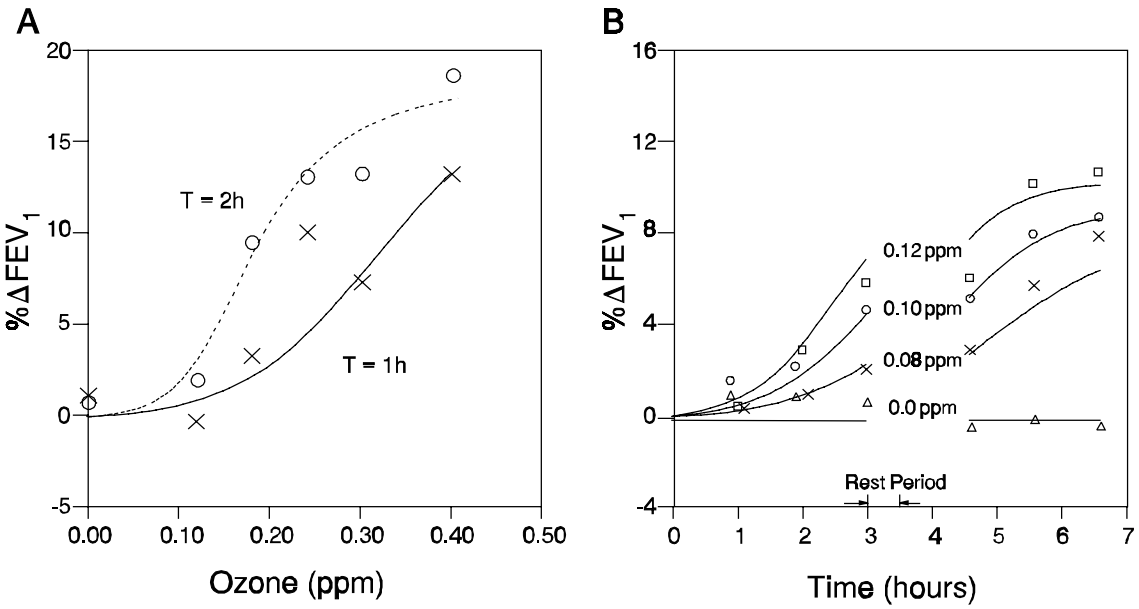

Figure 9-2. Predicted mean decrements in forced expiratory volume in 1 s for 1- and 2-h exposures to ozone with intermittent heavy exercise (A) and 6.6-h exposures with moderate prolonged exercise (B).

Source: McDonnell and Smith (1994).

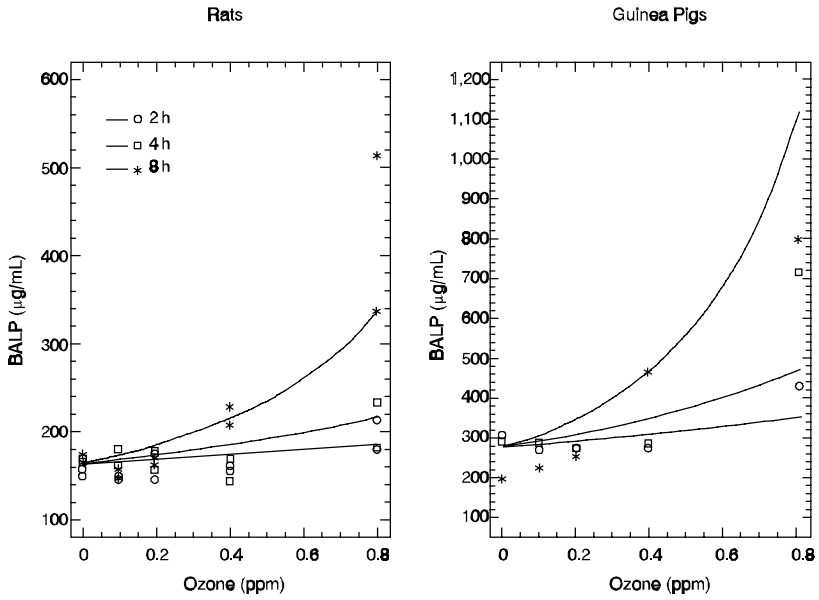

Figure 9-3. Derived means of BAL protein (BALP) denoted by symbols and the exponential model shown by lines as time of exposure varies from 2 to 8 h.

Source: Highfill et al. (1992).

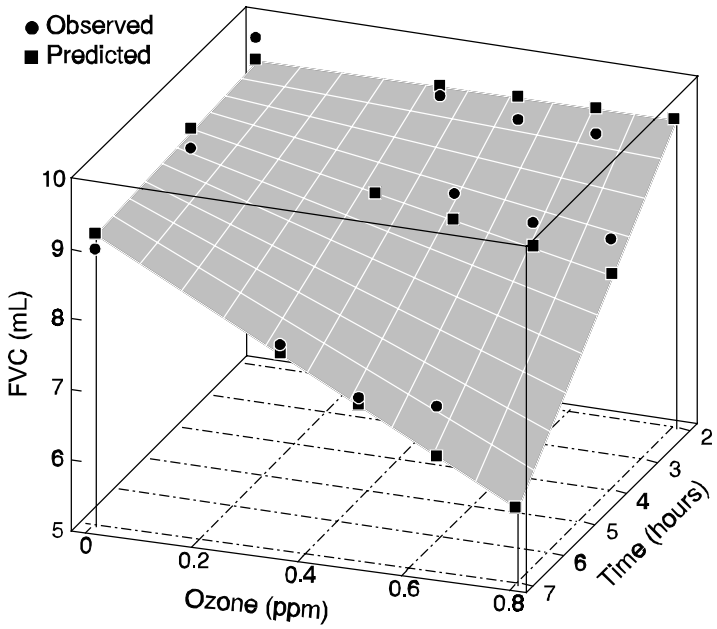

Figure 9-4. Predicted mean forced vital capacity for rats exposed to ozone while undergoing intermittent carbon dioxide-induced hyperpnea.

Source: Tepper et al. (1994).

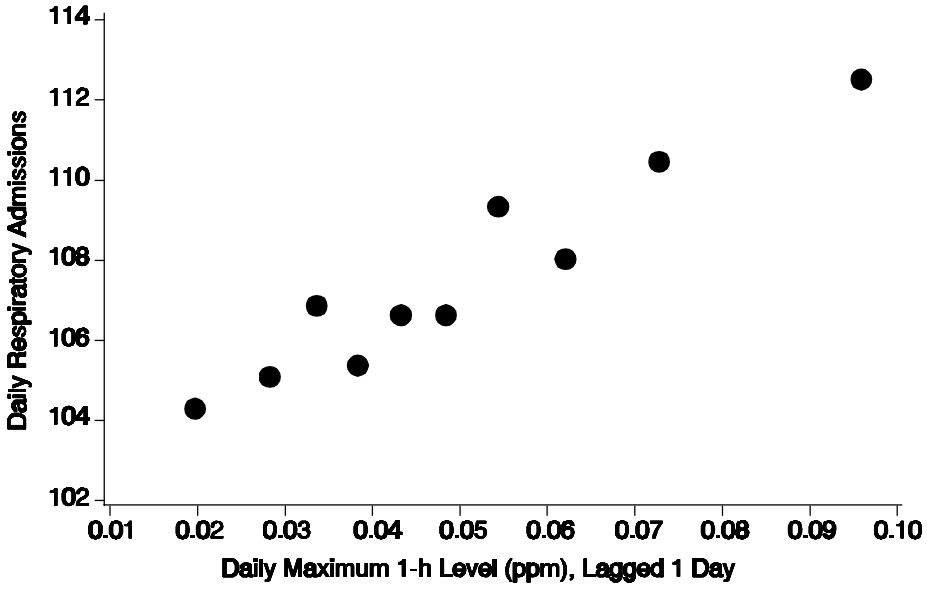

Figure 9-5. Average number of adjusted respiratory admissions among all 168 hospitals by decile of the daily 1-h maximum ozone level (ppm), lagged 1 day.

Source: Burnett et al. (1994)

8. Adams et al. (1981) predict lung function changes in humans as a function of the product of C × T × $\dot{V}_E$ for C = 0 to 0.4 ppm O_3, T = 30 to 80 min, and $\dot{V}_E$ = 33 or 66 L/min.
9. Rombout et al. (1989) predict the concentration of protein in BAL fluid of rats as a function of C (0.25 to 4.0 mg/m^3 O_3) and T (0 to 12 h) for daytime and nighttime exposures.
10. Highfill and Costa (1995) compare the fits of quadratic, exponential, and sigmoid-shaped models to published human lung function data and O_3 laboratory animal BAL data.
11. Thurston et al. (1994) predict hospital admissions in Toronto as a function of C (previous day 1-h O_3 maximum) for Toronto hospitals.

9.3.4.2 Prediction and Summary of Individual Responses

It is well known that considerable interindividual differences in the magnitude of response to O_3 exposure exist. The individual lung function and, to a lesser extent, respiratory symptom responses to O_3 have been demonstrated to be reproducible over a period of time, indicating that some individuals are consistently more responsive than others to O_3. The basis for these differences is not known, with the exception that young adults have been observed to be more responsive than older adults (see Figure 9-6).

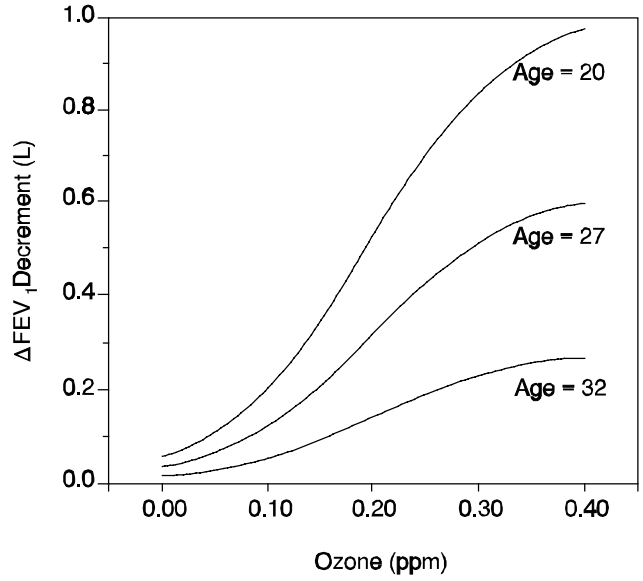

Figure 9-6. Predicted mean decrements in forced expiratory volume in 1 s (ΔFEV_1) following 2-h exposures to ozone while undergoing heavy intermittent exercise for three ages. (Note: To convert ΔFEV_1 to %ΔFEV_1, multiply by 22.2%.)

Source: McDonnell et al. (1993).

Calculation of group mean responses for a population that includes both more and less responsive individuals is useful for making inferences regarding the probability that a population effect is present or absent for a given exposure. Because the frequency distribution of individual responses to O_3 changes with changing exposure conditions, however, knowledge of the mean and variance of population responses does not provide reliable information on the distribution of individual responses for a given exposure, and, hence, is not particularly useful for estimating risks to members of the population. One method of presenting individual data is illustrated in Figure 9-7 in which histograms are presented for individual responses of subjects participating in four 6.6-h studies of low-level O_3 exposure.

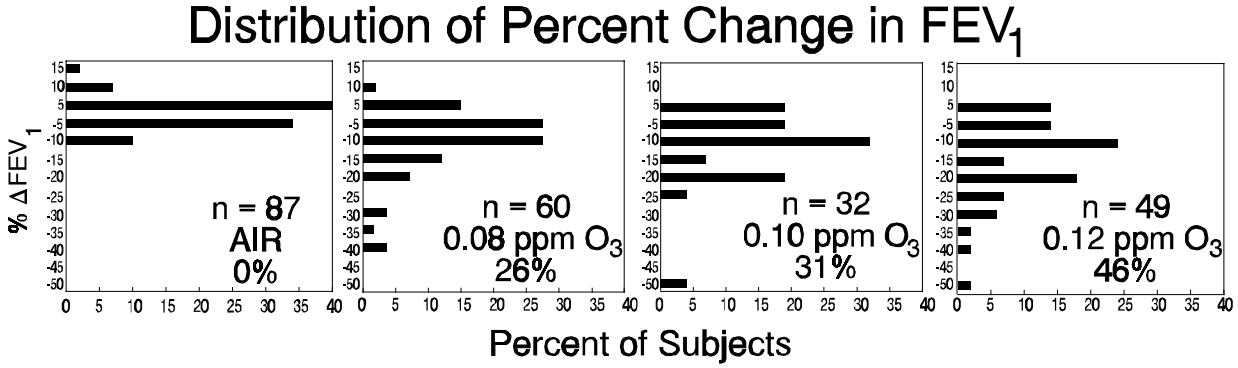

Figure 9-7. The distribution of response for 87 subjects exposed to clean air and at least one of 0.08, 0.10, or 0.12 ppm ozone (O_3). The O_3 exposures lasted 6.6 h, during which time the subjects exercised for 50 min of each hour, with a 35-min rest period at the end of the third hour. Decreases in forced expiratory volume in 1 s (FEV_1) are expressed as percent change from baseline. For example, the bar labeled, "−10" indicates the percent of subjects with a decrease in FEV_1 of >5% but ≤10%, and the bar labeled "5" indicates improvement in FEV_1 of >0% but ≤5%. Each panel of the figure indicates the percentage of subjects at each O_3 concentration with a decrease of FEV_1 in excess of 10%.

Similarly, the histograms of regression slopes of the lung function-O_3 concentration relationship for children participating in a camp study illustrate a large range of variability in response (Figure 9-8).

Another method that allows interpolation between observed data points involves definition of the effect of interest (e.g., a 10% decrement in FEV_1) and modeling of the proportion of individuals who experience such an effect as a function of exposure conditions. Figures 9-9 and 9-10 show the predicted proportion of individuals (humans) experiencing 10% FEV_1 decrements and respiratory symptom responses, respectively, as a function of C (0.0 to 0.4 ppm O_3) for independent studies conducted at either 1 or 2 h of exposure with heavy exercise.

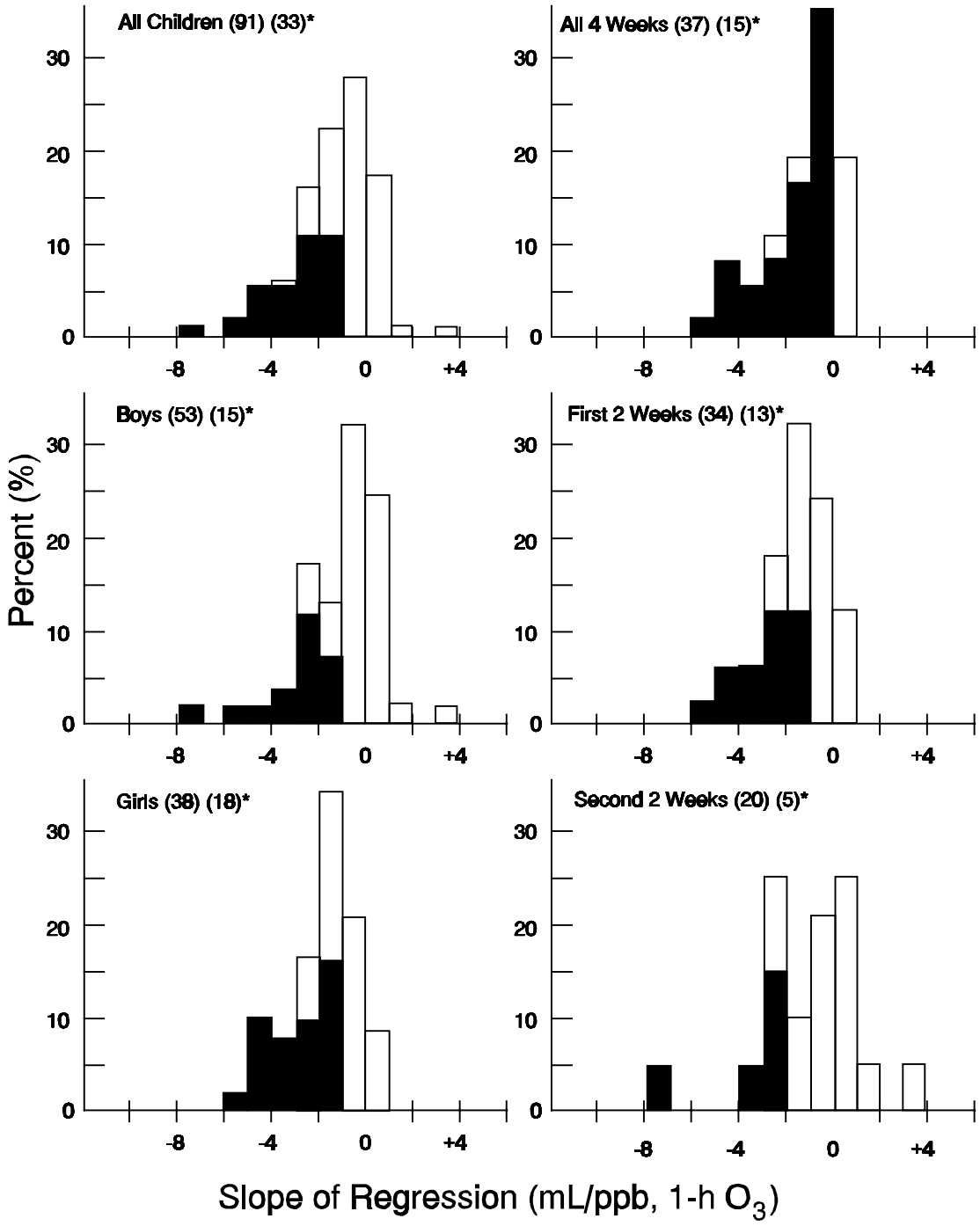

Figure 9-8. ***Histograms of regression slopes for FEV_1 versus 1-h ozone (O_3) concentration in children attending a summer camp in northwestern New Jersey. The numbers of children in each group are indicated in parentheses; an asterisk identifies the number of children with slopes that were significantly different from zero ($p < 0.05$). Shading represents the percent of significant ($p < 0.05$) slopes across the distributions.***

Source: Spektor et al. (1988).

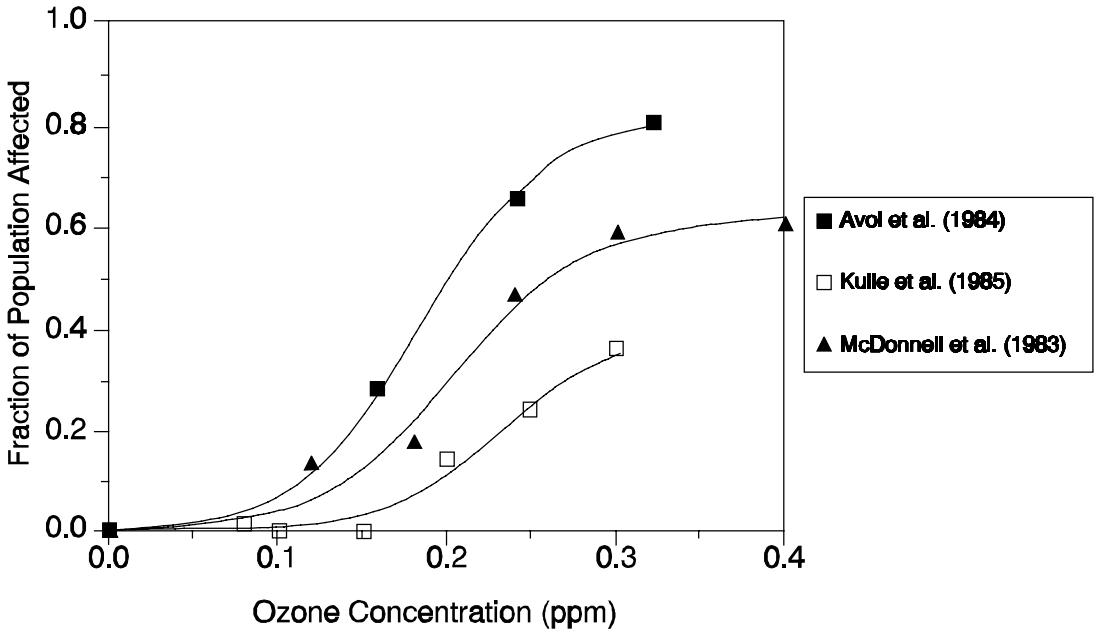

Figure 9-9. Proportion of heavily exercising individuals predicted to experience a 10% decrement in forced expiratory volume in 1 s following a 1- or 2-h exposure to ozone.

Source: U.S. Environmental Protection Agency (1989).

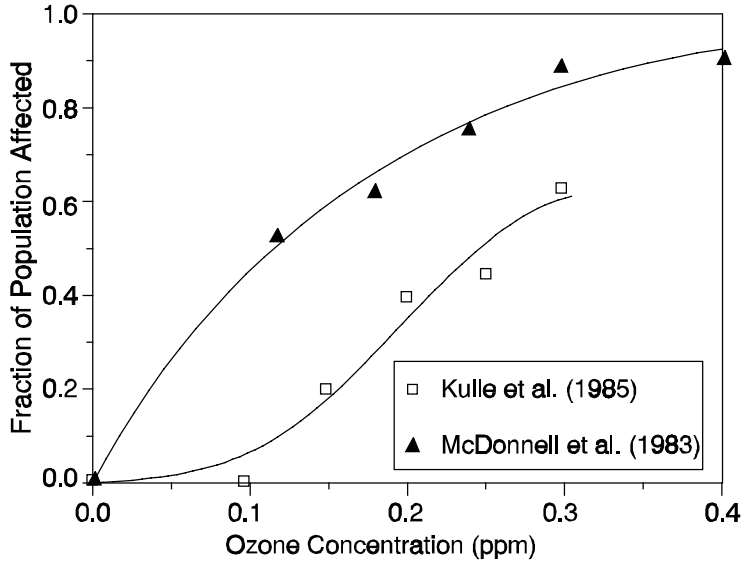

Figure 9-10. Proportion of heavily exercising individuals predicted to experience mild cough following a 2-h ozone exposure.

Source: U.S. Environmental Protection Agency (1989).

Predictions of the proportion of individuals experiencing 5, 10, or 15% FEV_1 decrements as a function of C (0.0 to 0.12 ppm O_3), T (1 to 6.6 h), at a specific age (24 years) for exposures with moderate exercise are shown in Figure 9-11.

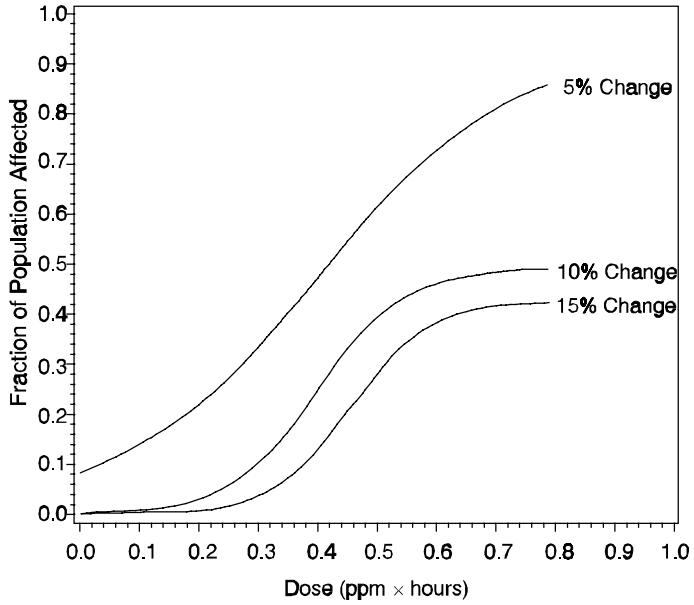

Figure 9-11. Proportion of moderately exercising individuals exposed to ozone for 6.6 h predicted to experience 5, 10, or 15% decrements in forced expiratory volume in 1 s as a function of C × T for age = 24 years.

Source: McDonnell et al. (1995).

As an example of differences between the mean and individual responses, it was stated earlier that exposure for 5.6 h to 0.08 ppm O_3 was the shortest duration for which a 5% mean decrement in FEV_1 was observed. For those same exposure conditions, 41, 17, and 10% of the subjects studied experienced FEV_1 decrements larger than 5, 10, and 15%, respectively.

The clinical significance of individual responses to O_3 exposure depends on the health status of the individual, the magnitude of the changes in pulmonary function, the severity of respiratory symptoms, and the duration of the response. Tables 9-1 and 9-2 categorize individual functional and symptomatic responses to O_3 exposure as normal (or none) and by increasing levels of severity in healthy persons and in persons with impaired respiratory systems, respectively. Pulmonary function responses are represented in these tables by changes in spirometry (e.g., FEV_1), SR_{aw}, and nonspecific bronchial responsiveness. Respiratory symptom responses include cough, pain on deep inspiration, and wheeze. The changes in spirometry that have been focused on most frequently are O_3-induced decrements in FEV_1 because they are easily quantified, have a continuous distribution, and have been used to provide most of the exposure-response relationships described in this section. The combined impact of both functional and symptomatic

Table 9-1. Gradation of Individual Responses to Short-Term Ozone Exposure in Healthy Persons[a]

Functional Response	None	Small	Moderate	Large
FEV_1	Within normal range (±3%)	Decrements of 3% to ≤10%	Decrements of >10% but <20%	Decrements of ≥20%
Nonspecific bronchial responsiveness[b]	Within normal range	Increases of <100%	Increases of ≤300%	Increases of >300%
Duration of response	None	<4 hours	>4 hours but ≤24 hours	>24 hours
Symptomatic Response	Normal	Mild	Moderate	Severe
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	<4 hours	>4 hours but ≤24 hours	>24 hours
Impact of Responses	Normal	Normal	Mild	Moderate
Interference with normal activity	None	None	A few sensitive individuals choose to limit activity	Many sensitive individuals choose to limit activity

[a]See text for discussion; see Appendix A for abbreviations and acronyms.
[b]An increase in nonspecific bronchial responsiveness of 100% is equivalent to a 50% decrease in PD_{20} or PD_{100} (see Chapter 7, Section 7.2.3).

responses to O_3 exposure generally is displayed as an interference with normal activity or a change in medical treatment (see Tables 9-1 and 9-2).

In healthy individuals, the importance attached to individual changes in FEV_1 and nonspecific bronchial responsiveness depends, in part, on the magnitude and persistence of the response, but it is also important to consider the circumstances in which changes in lung function occur with other responses. For example, a 20% decrement in FEV_1 or a 100 to 200% increase in SR_{aw} that is induced as a result of a nonspecific bronchial responsiveness test and one that is almost completely reversible within an hour is associated with little, if any, airway epithelial damage. If, in addition, there are no respiratory symptoms (except chest discomfort), then this response, in itself, would not be considered clinically significant. On the other hand, a smaller decrement in FEV_1 of 15%, accompanied by marked pain on deep inspiration and persistent cough that is reversed in approximately 24 h, may be considered clinically significant in some individuals. In other words, it is important to

Table 9-2. Gradation of Individual Responses to Short-Term Ozone Exposure in Persons with Impaired Respiratory Systems[a]

Functional Response	None	Small	Moderate	Large
FEV_1 change	Decrements of <3%	Decrements of 3 to ≤10%	Decrements of >10% but <20%	Decrements of ≥20%
Nonspecific bronchial responsiveness[b]	Within normal range	Increases of <100%	Increases of ≤300%	Increases of >300%
Airway resistance (SR_{aw})	Within normal range (±20%)	SR_{aw} increased <100%	SR_{aw} increased up to 200% or up to 15 cm H_2O/s	SR_{aw} increased >200% or more than 15 cm H_2O/s
Duration of response	None	<4 hours	>4 hours but ≤24 hours	>24 hours
Symptomatic Response	Normal	Mild	Moderate	Severe
Wheeze	None	With otherwise normal breathing	With shortness of breath	Persistent with shortness of breath
Cough	Infrequent cough	Cough with deep breath	Frequent spontaneous cough	Persistent uncontrollable cough
Chest pain	None	Discomfort just noticeable on exercise or deep breath	Marked discomfort on exercise or deep breath	Severe discomfort on exercise or deep breath
Duration of response	None	<4 hours	>4 hours, but ≤24 hours	>24 hours
Impact of Responses	Normal	Mild	Moderate	Severe
Interference with normal activity	None	Few individuals choose to limit activity	Many individuals choose to limit activity	Most individuals choose to limit activity
Medical treatment	No change	Normal medication as needed	Increased frequency of medication use or additional medication	Physician or emergency room visit

[a]See text for discussion; see Appendix A for abbreviations and acronyms.
[b]An increase in nonspecific bronchial responsiveness of 100% is equivalent to a 50% decrease in PD_{20} or PD_{100} (see Chapter 7, Section 7.2.3).

consider the pattern of responses and not simply to focus on a single marker of the effect of O_3.

The magnitude of individual changes can become more important in persons with impaired respiratory systems (e.g., asthmatics) who already have reduced baseline lung function. Any change in function that causes these individuals to drop below 40 to 50% of predicted would be considered clinically adverse. For example, O_3-induced changes in SR_{aw}, a measure of airway narrowing, are small and of minimal clinical significance in nonasthmatic individuals. Asthmatics, however, often have baseline airway narrowing and experience larger changes in SR_{aw} on exposure to O_3 than do nonasthmatics. Because of these baseline differences, the clinical significance of increases in SR_{aw} depends both on percent change from baseline and on absolute increases in SR_{aw}.

9.4 Effects of Long-Term Ozone Exposures

In both humans and test animals, the response to a single O_3 exposure nominally can be characterized by lung dysfunction, lung cell injury and inflammation, and leakage of plasma proteins into the airspace lumen. However, when such an exposure is repeated for several consecutive days, many of these effects appear to wane, suggesting attenuation or the development of tolerance to the continued intermittent challenge. In spite of this apparent state of attenuation, long-term O_3 exposures have been linked to subtle pulmonary effects, some of which have irreversible components, thereby enhancing concern about chronic effects. The following section will provide an overview attempting to synthesize the current understanding of the phenomenon of attenuation during brief, repeated exposures and the evidence for potential health impairments resulting from protracted exposures to this oxidant.

9.4.1 Repeated Exposures

It is well established that a brief exposure of laboratory rodents to an O_3 concentration, which causes minimal effects, will protect the animals from a subsequent lethal challenge of O_3 a week later. This phenomenon, called tolerance, bears a similarity to the pattern of attenuated nonlethal effects (sometimes referred to as "adaptation") observed in both human volunteers and animals when exposed to episodic levels of O_3 ($\leq$0.5 ppm) for 1 to 7 h/day over a succession of 5 or more days. Generally, over a 5-day exposure period, the effects of Day 1 are accentuated on Day 2 and diminish thereafter. Attenuation of the functional effects include spirometric deficits and associated symptoms as well as irritative alterations of breathing; nonspecific airway responsiveness, however, does not revert to normal levels. Measures of tissue effects that attenuate include inflammation and impaired phagocytic capabilities of alveolar macrophages. However, some evidence from animal studies suggests that tissue alterations persist, although the observed changes may be part of a transition to a chronically affected stage of the lung. Thus, in general, cell-associated indicators of injury or damage within the lung appear to diminish in spite of the continued O_3 exposure.

A number of mechanisms have been shown to be involved in the evolution of this "adapted" state. These mechanisms range from the replacement of sensitive cells in the alveolar lining (epithelium) by more resistant cells (with or without a thickened fluid barrier on the lumenal surface) to the enhancement of antioxidant metabolism providing cell resistance and more biochemical defenses at the lung surface. However, controlled human

studies show that after a 1-week period without O_3 exposure, subjects regain their spirometric responsiveness to O_3 challenge, although this abrupt transition between unresponsiveness and responsiveness appears less distinct in field-related studies. For example, studies of Southern Californians suggest that they are significantly less responsive to the spirometric effects of an acute episodic-like controlled challenge with O_3 when studied for a period after the "high" O_3 season than after the relatively "low" O_3 season. Likewise, there is some evidence that O_3-exposed urban populations are also somewhat more resistant to the oxidant than populations that receive minimal exposure. This would appear to be in conflict with hospital admissions data suggesting the aggravation of respiratory diseases, like asthma, within such populations. It remains to be shown whether these latter data reflect the responsiveness of a sensitive subpopulation, perhaps less adapted or having less reserve function.

9.4.2 Prolonged Exposures

Most long-term exposure studies in animals have evaluated structural and functional changes. In the few investigations of the immune system or antibacterial host defenses, prolonged exposures of animals either caused no effects or did not increase the magnitude of effects observed after acute exposures. Thus, the following discussion centers on the larger body of knowledge on other endpoints.

Epidemiologic studies attempting to associate chronic lung effects in humans with long-term O_3 exposure provide only suggestive evidence that such a linkage exists. Most studies have been cross-sectional in design and have been compromised by incomplete control of confounding variables and inadequate exposure information. Other studies have attempted to follow variably exposed groups prospectively. Studies of such design have been conducted in communities of the Southwest Air Basin as well as in Canada where comparisons could be drawn between lung function changes over several years in populations from high- or low-oxidant pollution. The findings suggest small, but consistent decrements in lung function among inhabitants of the more highly polluted communities. However, associations between O_3 and other copollutants and, in some cases, problems with study population loss undermine the confidence in the study conclusions. Likewise, recent associations found between O_3 and the incidence and severity of asthma over a decade of study, although derived from well-designed studies, also tend to be weakened by the colinearity of O_3 with other air pollutants. Nevertheless, in all of the studies assessing lung function, the pattern of dysfunction associated with the long-term exposure has been consistent with the functional and structural abnormalities seen in laboratory animal studies.

The advantage of laboratory animal studies is the ability to examine closely the distribution and intensity of the O_3-induced morphologic changes that have been identified throughout the respiratory tract (see Chapter 6, Section 6.2.4). Indeed, cells of the nose, like the distal lung, clearly are affected by O_3. Perhaps of greater health concern are the lesions that occur in the small airways and in the centriacinar regions of the lung where the alveoli meet the distal airways (Figure 9-12). Altered function of the distal airways, the proximal conduits of air to the gas-exchange regions, can result in reduced communication of fresh air with the alveoli and air-trapping. In fact, chronic O_3 lesions as found in animal studies are reminiscent of the earliest lesions found in respiratory bronchiolitis, some of which may progress to fibrotic lung disease (Kuhn et al., 1989; King, 1993).

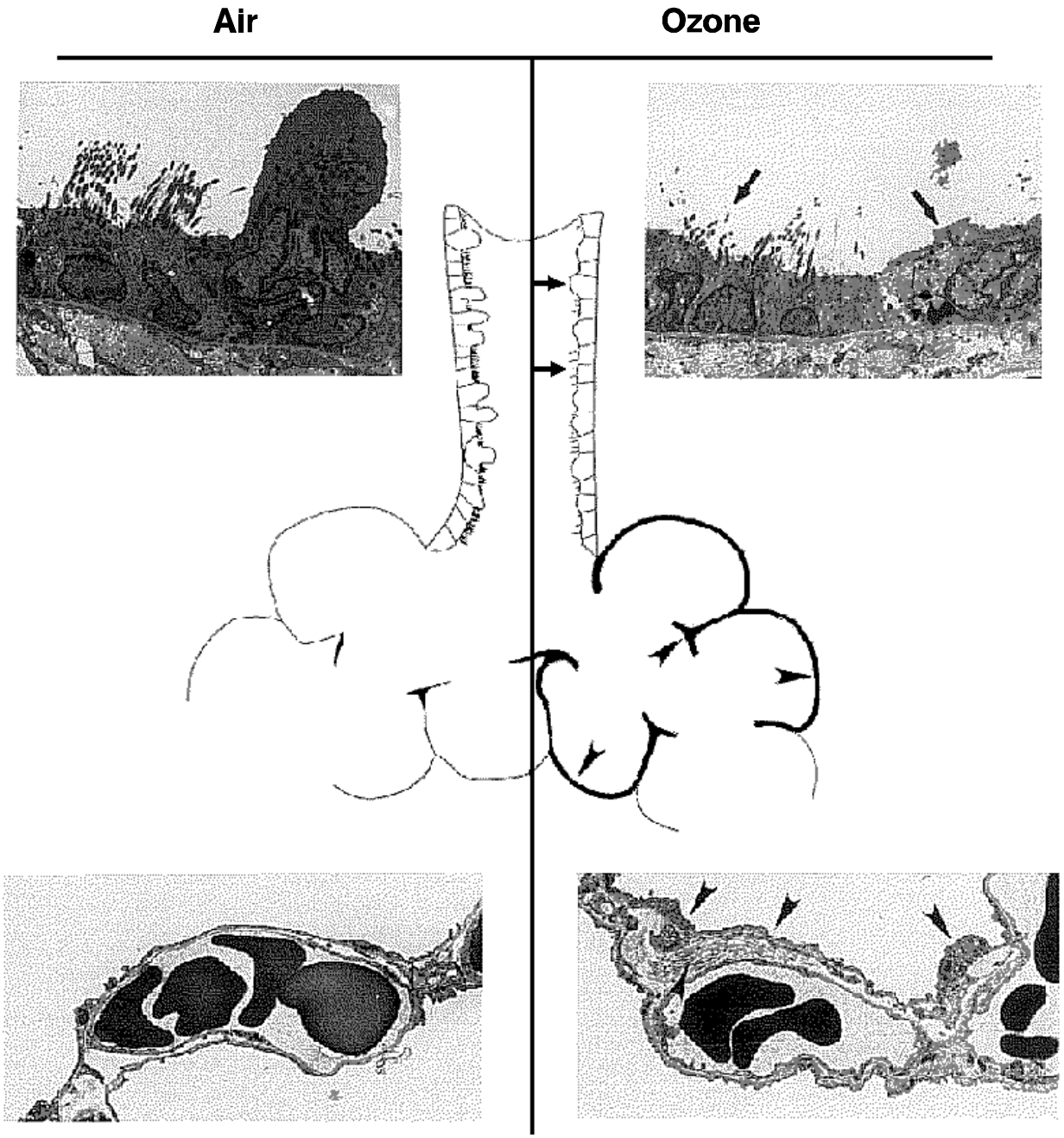

Figure 9-12. A summary of the morphologic lesions found in the terminal bronchioles and centriacinar region (CAR) of the lung following exposure of laboratory rats to filtered air or a simulated ambient pattern of ozone for up to 78 weeks. In the terminal bronchiole, the sizes of the dome of Clara cells became smaller with ozone exposure, and the number of cilia is reduced (arrows). In the CAR, the epithelium becomes thicker, and accumulation of collagen fibers occurs (arrow heads).

Source: Chang et al. (1992).

The O_3-induced inflammation, cell damage, and altered permeability of epithelial cells lining the respiratory tract allow exudation of fluid, cells, and cellular debris from plasma into lung tissue. The magnitude of intraluminal exudation associated with injury correlates with the initial epithelial necrosis and release of inflammatory mediators. As shown in Figure 9-13, the temporal pattern of effects during and after a chronic exposure is complex. During the early days of exposure, the end-airway lumenal and interstitial inflammation peaks, and, thereafter, appears to subside at a lower plateau of activity sometimes referred to as a "smoldering" lesion. Several cytokines remain elevated beyond the apparent adaptation phase of the response and may be linked conceptually to the development of chronic lesions in the distal lung. To date, however, a clear association of these BAL-derived mediators and cells with long-term toxicity has not been demonstrated. Some evidence of molecular changes within the matrix of the lung may also link to the chronic effects, but these too remain poorly defined. When exposures to O_3 continue for weeks or months, the diminished O_3-induced exudative response in the distal bronchoalveolar areas is supplanted by hyperplastic epithelia in the alveoli and end-airways. Damaged cells in centriacinar alveoli are replaced by metabolically active progenitor cells that are more resistant to oxidant challenge. Junctional areas between conducting and gas-exchange regions, where the O_3 changes are typically most intense, also undergo epithelial hyperplasia, giving the appearance that airway cells are extending into the mouth of the alveolus, hence the term "bronchiolization". The functional result of this concentration-dependent process is the effective elongation of distal bronchioles, which functionally may alter air distribution within the lung during breathing. These hyperplastic cells also are believed to be more resistant to O_3. When exposure to O_3 ceases, most, but not all, of the hyperplasia appears to reverse with time.

In contrast, within the underlying interstitium (tissue between blood and air spaces) of the affected centriacinar region, proliferating fibroblasts appear to evolve excess noncellular fibrous matrices, which may be only partially reversible and may, in fact, progress after removal from O_3 exposure. This would suggest that O_3 can initiate focal interstitial fibrosis of the lung at the regions where O_3 causes epithelial cell damage as a prelude to chronic degenerative lung disease. The crucial question, then, is whether this latter irreversible process, which clearly occurs at relatively high O_3 concentrations, occurs at ambient levels to which humans are typically exposed, in many cases, over a lifetime. Unfortunately, comparable morphologic data from humans residing in O_3-polluted areas are lacking.

Studies of prolonged O_3 exposures in monkeys and rats reveal generally similar morphologic responses, although it appears that the monkey exhibits somewhat more tissue injury than does the rat under roughly similar exposure conditions. Interspecies comparisons of dosimetric data indicate that the monkey, with its similarity to the human in distal airway structure, provides data that may best reflect the potential effects of O_3 in humans exercising out of doors. As such, monkeys exposed to O_3 at 0.15 ppm for 8 h each day for 6 to 90 days exhibit significant distal airway remodeling. Rats show similar but more modest changes at 0.25 ppm O_3 after exposures of longer duration, up to 18 mo and beyond (near-lifetime). The chronic distal lung and airway alterations appear consistent with incipient peribronchiolar fibrogenesis within the interstitium. Attempts to correlate functional deficits have been variable, perhaps due in part to the degree and distribution of the lesions and the general insensitivity of most measures of the distal lung function. The interstitial changes may progress, however. Moreover, one recent primate study revealed evidence that

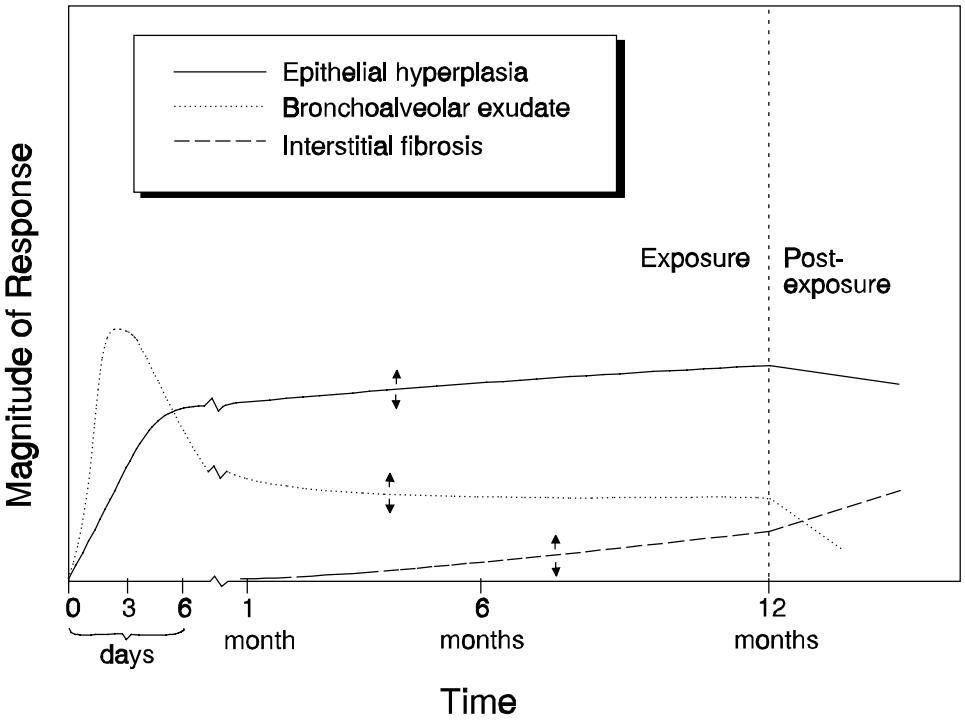

Figure 9-13. Schematic comparison of the duration-response profiles for epithelial hyperplasia, bronchoalveolar exudation, and interstitial fibrosis in the centriacinar region of lung exposed to a constant low concentration of ozone.

Source: Dungworth (1989).

intermittent challenge with a pattern of O_3 exposure more reflective of seasonal episodes, with extended periods of clean air in between extended periods of O_3, actually leads to greater injury. The reasons for this are unclear, but may relate to the known loss of tolerance that occurs in both humans and animal test species with removal of the oxidant burden.

In conclusion, the collective toxicologic data on chronic exposure to O_3 garnered in animal exposure and human population studies have some ambiguities. What is clear is that the distribution of the O_3 lesions is roughly similar across species, is, in part, concentration dependent (and perhaps time or exposure-pattern dependent), and, under certain conditions, has irreversible structural attributes. What is unclear is whether ambient exposure scenarios encountered by humans result in similar lesions and whether there are resultant functional or impaired health outcomes, particularly because the human exposure scenario may involve much longer exposures than can be studied in the laboratory. The epidemiologic lung function data generally parallel those of the animal studies, but they lack the confidence of O_3 exposure history and are frequently confounded by personal or copollutant variables.

9.4.3 Genotoxicity and Carcinogenicity of Ozone

Numerous in vitro exposure studies suggest that O_3 has either weak or no potential to cause mutagenic, cytogenetic, or cellular transformation effects. Most of these experiments utilized high concentrations of O_3 (>5.0 ppm). Because of the exposure systems used, there are unknowns about the formation of artifacts and the dose of O_3. Therefore, these studies are not very useful in health assessment. Cytogenetic effects have been observed in some, but not all, laboratory animal and human studies of short-term O_3 exposure. However, well-designed human clinical cytogenetic studies were negative.

Until recently, in vivo exposure studies of carcinogenicity, with and without co-exposure to known carcinogens, were either negative or ambiguous. A well-designed cancer bioassay study has recently been completed by the National Toxicology Program (NTP) using male and female Fischer 344/N rats and $B6C3F_1$ mice. Animals were exposed for 2 years to 0.12, 0.5, and 1.0 ppm O_3 (6 h/day, 5 days/week). A similar lifetime exposure was conducted, but 0.12 ppm was not used. The NTP evaluated the weight-of-evidence for this study; they found "no evidence" of carcinogenicity in rats but reported "equivocal evidence" of carcinogenicity in O_3-exposed male mice and "some evidence" of carcinogenic activity in O_3-exposed female mice. The increases in adenomas and carcinomas were observed only in the lungs. There was no concentration response. In the male mice, the incidence of neoplasms in the 2-year study was not elevated significantly by O_3 and was within the range of historical controls. The lifetime exposure resulted in an increased incidence of carcinomas that was not statistically significant. When the female mouse data from the two exposure regimens (at 1.0 ppm) were combined, there was a statistically significant increase (almost double) in neoplasms. In a companion study, male rats were treated with a tobacco carcinogen and exposed for 2 years to 0.5 ppm O_3. Ozone did not affect the response and, therefore, had no tumor promoting activity.

In summary, only chronic exposure to a high concentration of O_3 (1.0 ppm) has been shown to evoke a limited degree of carcinogenic activity in the females of one strain of mice. Rats were not affected. Furthermore, there was no concentration response, and there is inadequate information from other research to provide mechanistic support for the finding in mice. Thus, the potential for animal carcinogenicity is uncertain.

9.5 Effects of Combined Pollutant Exposures

In ambient air, people are exposed to mixtures of pollutants, making it important to understand interactions. Epidemiological studies, which inherently evaluate O_3 as part of complex mixtures, are discussed in other subsections dealing with classes of effects. In the laboratory it becomes possible to sort out the role of O_3 in simple mixtures. Complex mixtures are typically not investigated in the laboratory because, even if only six pollutants were involved, the experimental design required to unequivocally sort out which pollutant or pollutant interactions were responsible for the responses or portions of the responses could require as many as 719 additional separate experiments, even if the concentrations of the six pollutants remained the same.

The summary will focus only on binary mixtures because these are by far the predominant type of experiments. Responses to a binary pollutant mixture may represent the sum of the independent responses to the two chemicals (i.e., an additive response). If there is some interaction between either the two responses or the two pollutants, the resultant response

could be larger than additive (synergism) or smaller than additive (antagonism). Interaction between pollutants could result in the production of a more or less toxic byproduct. Alternatively, the response to one pollutant could magnify the response to the other pollutant or could interfere with or block the action of the other pollutant. Binary mixture studies fall into two categories, simultaneous and sequential exposures. In the simultaneous exposures, both the responses and the pollutants can interact. In the sequential exposures, it is primarily the responses that would interact.

In general, controlled human studies of O_3 mixed with other pollutants show no more than an additive response with symptoms or spirometry as an endpoint. This applies to O_3 in combination with nitrogen dioxide (NO_2), SO_2, sulfuric acid (H_2SO_4), nitric acid (HNO_3), or carbon monoxide (CO). Indeed, at the levels of copollutants used in human exposure studies, the responses can be attributed primarily to O_3. In one study, exposure to O_3 increased airway responsiveness to SO_2 in asthmatics. Similarly, other pollutants that may increase airway responsiveness could augment the effect of O_3 on airway responsiveness.

The relatively large number of animal studies of O_3 in mixture with NO_2 and H_2SO_4 shows that additivity, synergism, and antagonism can result, depending on the exposure regimen and the endpoint studied. The numerous observations of synergism are of concern, but the interpretation of most of these studies relative to the real world is confounded by unrealistic exposure designs. For example, ambient concentrations of O_3 often were combined with levels of copollutants substantially higher than ambient, creating the possibility that mechanisms of toxicity unlikely in the real world contributed to the experimental outcome. Nevertheless, the data support a hypothesis that coexposure to pollutants, each at innocuous or low-effect levels, may result in effects of significance.

9.6 Conclusions

This section summarizes the primary conclusions derived from an integration of the known effects of O_3 provided by animal toxicological, human clinical, and epidemiological studies.

1. What are the effects of short-term (<8-h) exposures to ozone?

Recent epidemiology studies addressing the effects of short-term ambient exposure to O_3 in the population have yielded significant associations with a wide range of health outcomes, including lung function decrements, aggravation of preexisting respiratory disease, increases in daily hospital admissions and emergency department visits for respiratory causes, and increased mortality. Results from lung function epidemiology studies are generally consistent with the experimental studies in laboratory animals and humans.

Short-term O_3 exposure of laboratory animals and humans causes changes in pulmonary function, including tachypnea (rapid, shallow breathing), decreased lung volumes and flows, and increased airway responsiveness to nonspecific stimuli. Increased airway resistance occurs in both humans and laboratory animals, but typically at higher exposure levels than other functional endpoints. In addition, adult human subjects experience O_3 induced symptoms of airway irritation such as cough or pain on deep inspiration. The changes in pulmonary function and respiratory symptoms occur as a function of exposure concentration, duration, and level of exercise. Adult human subjects with mild asthma have qualitatively similar responses in lung volume and airway responsiveness to

bronchoconstrictor drugs as nonasthmatics. Respiratory symptoms are also similar, but wheezing is a prevalent symptom in O_3-exposed asthmatics in addition to the other demonstrated symptoms of airway irritation. Airway resistance, however, increases relatively more in asthmatics from an already higher baseline. Recovery from the effects of O_3 on pulmonary function and symptoms is usually complete within 24 h of the end of exposure, although other responses may persist somewhat longer.

- An association between daily mortality and O_3 concentration for areas with high O_3 levels (e.g., Los Angeles) has been suggested, although the magnitude of such an effect is unclear.
- Increased O_3 levels are associated with increased hospital admissions and emergency department visits for respiratory causes. Analyses from data in the Northeastern United States suggest that O_3 air pollution is associated with a substantial portion (on the order of 10 to 20%) of all summertime respiratory hospital visits and admissions.
- Pulmonary function in children at summer camps in southern Ontario, Canada, in the northeastern United States, and in Southern California is associated with O_3 concentration. Meta-analysis indicates that a 0.50-mL decrease in FEV_1 is associated with a 1 ppb increase in O_3 concentration. For preadolescent children exposed to 120 ppb (0.12 ppm) ambient O_3, this amounts to an average decrement of 2.4 to 3.0% in FEV_1. Similar responses are reported for children and adolescents exposed to O_3 in ambient air or O_3 in purified air for 1 to 2 h while exercising.
- Pulmonary function decrements are generally observed in healthy subjects (8 to 45 years of age) after 1 to 3 h of exposure as a function of the level of exercise performed and the O_3 concentration inhaled during the exposure. Group mean data from numerous controlled human exposure and field studies indicate that, in general, statistically significant pulmonary function decrements beyond the range of normal measurement variability (e.g., 3 to 5% for FEV_1) occur
  (1) at >0.50 ppm O_3 when at rest,
  (2) at >0.37 ppm O_3 with light exercise (slow walking),
  (3) at >0.30 ppm O_3 with moderate exercise (brisk walking),
  (4) at >0.18 ppm O_3 with heavy exercise (easy jogging), and
  (5) at >0.16 ppm O_3 with very heavy exercise (running).
  Smaller group mean changes (e.g., <5%) in FEV_1 have been observed at lower O_3 concentrations than those listed above. For example, FEV_1 decrements have been shown to occur with very heavy exercise in healthy adults at 0.15 to 0.16 ppm O_3, and such effects may occur in healthy young adults at levels as low as 0.12 ppm. Also, pulmonary function decrements have been observed in children and adolescents at concentrations of 0.12 and 0.14 ppm O_3 with heavy exercise. Some individuals within a study may experience FEV_1 decrements in excess of 15% under these exposure conditions, even when the group mean decrement is less than 5%.
- For exposures of healthy subjects performing moderate exercise during longer duration exposures (6 to 8 h), 5% group mean decrements in FEV_1 were observed at
  (1) 0.08 ppm O_3 after 5.6 h,
  (2) 0.10 ppm O_3 after 4.6 h, and

(3) 0.12 ppm O_3 after 3 h.

For these same subjects, 10% group mean FEV_1 decrements were observed at 0.12 ppm O_3 after 5.6 and 6.6 h. As in the shorter duration studies, some individuals experience changes larger than those represented by the group mean changes.

- An increase in the incidence of cough has been reported at O_3 concentrations as low as 0.12 ppm in healthy adults during 1 to 3 h of exposure with very heavy exercise. Other respiratory symptoms, such as pain on deep inspiration, shortness of breath, and lower respiratory scores (a combination of several symptoms), have been observed at 0.16 to 0.18 ppm O_3 with heavy and very heavy exercise. Respiratory symptoms also have been observed following exposure to 0.08, 0.10, and 0.12 ppm O_3 for 6.6 h with moderate levels of exercise.
- Increases in nonspecific airway responsiveness in healthy adults have been observed after 1 to 3 h of exposure to 0.40 ppm, but not 0.20 ppm, O_3 at rest and have been observed at concentrations as low as 0.18 ppm, but not to 0.12 ppm, O_3 during exposure with very heavy exercise. Increases in nonspecific airway responsiveness during 6.6-h exposures with moderate levels of exercise have been observed at 0.08, 0.10, and 0.12 ppm O_3.

Short-term O_3 exposure of laboratory animals and humans disrupts the barrier function of the lung epithelium, permitting materials in the airspaces to enter lung tissue, allowing cells and serum proteins to enter the airspaces (inflammation), and setting off a cascade of responses.

- Increased levels of PMNs and protein in lung lavage fluid have been observed following exposure of healthy adults to 0.20, 0.30, and 0.40 ppm with very heavy exercise and have not been studied at lower concentrations for 1- to 3-h exposures. Increases in lung lavage protein and PMNs also have been observed at 0.08 and 0.10 ppm O_3 during 6.6-h exposures with moderate exercise; lower concentrations have not been tested.

Short-term O_3 exposure of laboratory animals and humans impairs alveolar macrophage clearance of viable and nonviable particles from the lungs and decreases the effectiveness of host defenses against bacterial lung infections in animals and perhaps humans. The ability of alveolar macrophages to engulf microorganisms is decreased in humans exposed to 0.08 and 0.10 ppm O_3 for 6.6 h with moderate exercise.

2. What are the effects of repeated, short-term exposures to ozone?

During repeated short-term exposures, some of the O_3-induced responses are partially or completely attenuated. Over a 5-day exposure, pulmonary function changes are typically greatest on the second day, but return to control levels by the fifth day of exposure. Most of the inflammatory markers (e.g., PMN influx) also attenuate by the fifth day of exposure, but markers of cell damage (e.g., lactate dehydrogenase enzyme activity) do not attenuate and continue to increase. Attenuation of lung function decrements is reversed following 7 to 10 days without O_3. Some inflammatory markers are also reversed during this time period, but others still show attenuation even after 20 days without O_3. The mechanisms and impacts involved in attenuation are not known, although animal studies show that the underlying cell damage continues throughout the attenuation process. In addition, attenuation may alter the normal distribution of O_3 within the lung, allowing more O_3 to reach sensitive

regions, possibly affecting normal lung defenses (e.g., PMN influx in response to inhaled microorganisms).

3. What are the effects of long-term exposures to ozone?

Available data indicate that exposure to O_3 for months and years causes structural changes in several regions of the respiratory tract, but effects may be of the greatest importance in the centriacinar regions (where the alveoli and conducting airways meet); this region typically is affected in most chronic airway diseases of the human lung. This information on O_3 effects in the distal lung is extrapolated from animal toxicological studies because, to date, comparable data are not available from humans. The apparent lack of reversal of effects during periods of clean air exposure raises concern that seasonal exposures may have a cumulative impact over many years. The role of adaptive processes in this response is unknown but may be critically dependent on the temporal frequency or profile of exposure. Furthermore, the interspecies diversity in apparent sensitivity to the chronic effects of O_3 is notable, with the rat representing the lower limit of response, and the monkey the upper limit. Epidemiological studies attempting to associate chronic health effects in humans with long-term O_3 exposure provide only suggestive evidence that such a linkage exists.

Long-term exposure in the females of one strain of mice to high O_3 levels (1 ppm) caused a small, but statistically significant increase in lung tumors. There was no concentration-response relationship, and rats were not affected. Genotoxicity data are either negative or weak. Given the nature of the database, potential carcinogenicity in animals is uncertain. Ozone did not show tumor-promoting activity in a chronic rat study (at 0.5 ppm O_3).

4. What are the effects of binary pollutant mixtures containing ozone?

Combined data from laboratory animal and controlled human exposure studies of O_3 support the hypothesis that coexposure to pollutants, each at low-effect levels, may result in effects of significance. The data from human studies of O_3 in combination with NO_2, SO_2, H_2SO_4, HNO_3, or CO show no more than an additive response on lung spirometry or respiratory symptoms. The larger number of laboratory animal studies with O_3 in mixture with NO_2 and H_2SO_4 show that effects can be additive, synergistic, or even antagonistic, depending on the exposure regimen and the endpoint studied. This issue of exposure to copollutants remains poorly understood, especially with regard to potential chronic effects.

5. What population groups are at risk as a result of exposure to ozone?

Identification of population groups that may show increased sensitivity to O_3 is based on their (1) biological responses to O_3, (2) preexisting lung disease (e.g., asthma), (3) activity patterns, (4) personal exposure history, and (5) personal factors (e.g., age, nutritional status).

The predominant information on the health effects of O_3 noted above comes from clinical and field studies on healthy, nonsmoking, exercising subjects, 8 to 45 years of age. These studies demonstrate that, among this group, there is a large variation in sensitivity and responsiveness to O_3, with at least a 10-fold difference between the most and least responsive individuals. Individual sensitivity to O_3 also may vary throughout the year, related to seasonal variations in ambient O_3 exposure. The specific factors that contribute to this large intersubject variability, however, remain undefined. Although differences may be due to the

dosimetry of O_3 in the respiratory tract, available data show little difference on O_3 deposition in the lungs for inhalation through the nose or mouth.

Daily life studies reporting an exacerbation of asthma and decrease in peak expiratory flow rates, particularly in asthmatic children, appear to support the controlled studies; however, those studies may be confounded by temperature, particle or aeroallergen exposure, and asthma severity of the subjects or their medication use. In addition, field studies of summertime daily hospital admissions for respiratory causes show a consistent relationship between asthma and ambient levels of O_3 in various locations in the Northeastern United States, even after controlling for independent contributing factors. Controlled studies on mild asthmatics suggest that they have similar lung volume responses but greater airway resistance changes to O_3 than nonasthmatics. Furthermore, limited data from studies of moderate asthmatics suggest that this group may have greater lung volume responses than nonasthmatics.

Other population groups with preexisting limitations in pulmonary function and exercise capacity (e.g., chronic obstructive pulmonary disease, chronic bronchitis, ischemic heart disease) would be of primary concern in evaluating the health effects of O_3. Unfortunately, not enough is known about the responses of these individuals to make definitive conclusions regarding their relative responsiveness to O_3. Indeed, functional effects in these individuals with reduced lung function may have greater clinical significance than comparable changes in healthy individuals.

Currently available data on personal factors or personal exposure history known or suspected of influencing responses to O_3 follow.

- Human studies have identified a decrease in pulmonary function responsiveness to O_3 with increasing age, although symptom rates remain similar. Toxicological studies are not easily interpreted but suggest that young animals are not more responsive than adults.
- Available toxicological and human data have not conclusively demonstrated that males and females respond differently to O_3. If gender differences exist for lung function responsiveness to O_3, they are not based on differences in baseline pulmonary function.
- Data are not adequate to determine whether any ethnic or racial group has a different distribution of responsiveness to O_3. In particular, the responses of nonwhite asthmatics have not been investigated.
- Information derived from O_3 exposure of smokers is limited. The general trend is that smokers are less responsive than nonsmokers. This reduced responsiveness may wane after smoking cessation.
- Although nutritional status (e.g., vitamin E deficiency) makes laboratory rats more susceptible to O_3-induced effects, it is not clear if vitamin E supplementation has an effect in human populations. Such supplementation has no or minimal effects in animals. The role of such antioxidant vitamins in O_3 responsiveness, especially their deficiency, has not been well studied.

Based on information presented in this document, the population groups that have demonstrated increased responsiveness to ambient concentrations of O_3 consist of exercising, healthy and asthmatic individuals, including children, adolescents, and adults.

References

Adams, W. C.; Savin, W. M.; Christo, A. E. (1981) Detection of ozone toxicity during continuous exercise via the effective dose concept. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 51: 415-422.

Avol, E. L.; Linn, W. S.; Venet, T. G.; Shamoo, D. A.; Hackney, J. D. (1984) Comparative respiratory effects of ozone and ambient oxidant pollution exposure during heavy exercise. J. Air Pollut. Control Assoc. 34: 804-809.

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Carr, W.; Zeitel, L.; Weiss, K. (1992) Variations in asthma hospitalizations and deaths in New York City. Am. J. Public Health 82: 59-65.

Chang, L.-Y.; Huang, Y.; Stockstill, B. L.; Graham, J. A.; Grose, E. C.; Ménache, M. G.; Miller, F. J.; Costa, D. L.; Crapo, J. D. (1992) Epithelial injury and interstitial fibrosis in the proximal alveolar regions of rats chronically exposed to a simulated pattern of urban ambient ozone. Toxicol. Appl. Pharmacol. 115: 241-252.

Cherniak, R. M.; Banks, D. E.; Bell, D. Y.; Davis, G. S.; Hughes, J. M.; King, T. E., Jr. (1990) Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. Am. Rev. Respir. Dis. 141(suppl.): S169-S202.

Dungworth, D. L. (1989) Noncarcinogenic responses of the respiratory tract to inhaled toxicants. In: McClellan, R. O.; Henderson, R. F., eds. Concepts in inhalation toxicology. New York, NY: Hemisphere Publishing Corp.; pp. 273-298.

Evans, R., III; Mullally, D. I.; Wilson, R. W.; Gergen, P. J.; Rosenberg, H. M.; Grauman, J. S.; Chevarley, F. M.; Feinleib, M. (1987) National trends in the morbidity and mortality of asthma in the US. Prevalence, hospitalization and death from asthma over two decades: 1965-1984. Chest 91(suppl.): 65S-74S.

Folinsbee, L. J.; Drinkwater, B. L.; Bedi, J. F.; Horvath, S. M. (1978) The influence of exercise on the pulmonary function changes due to exposure to low concentrations of ozone. In: Folinsbee, L. J.; Wagner, J. A.; Borgia, J. F.; Drinkwater, B. L.; Gliner, J. A.; Bedi, J. F., eds. Environmental stress: individual human adaptations. New York, NY: Academic Press; pp. 125-145.

Hazucha, M. J. (1987) Relationship between ozone exposure and pulmonary function changes. J. Appl. Physiol. 62: 1671-1680.

Highfill, J. W.; Costa, D. L. (1995) Statistical response models for ozone exposure: their generality when applied to human spirometric and animal permeability functions of the lung. J. Air Waste Manage. Assoc. 45: 95-102.

Highfill, J. W.; Hatch, G. E.; Slade, R.; Crissman, K. M.; Norwood, J.; Devlin, R. B.; Costa, D. L. (1992) Concentration-time models for the effects of ozone on bronchoalveolar lavage fluid protein from rats and guinea pigs. Inhalation Toxicol. 4: 1-16.

King, T. E., Jr. (1993) Bronchiolitis. In: Schwarz, M. I.; King, T. E., Jr., eds. Interstitial lung disease. 2nd ed. St. Louis, MO: Mosby Year Book; pp. 463-495.

Kuhn, C., III; Boldt, J.; King, T. E., Jr.; Crouch, E.; Vartio, T.; McDonald, J. A. (1989) An immunohistochemical study of architectural remodeling and connective tissue synthesis in pulmonary fibrosis. Am. Rev. Respir. Dis. 140: 1693-1703.

Kulle, T. J.; Sauder, L. R.; Hebel, J. R.; Chatham, M. D. (1985) Ozone response relationships in healthy nonsmokers. Am. Rev. Respir. Dis. 132: 36-41.

McDonnell, W. F.; Smith, M. V. (1994) Description of acute ozone response as a function of exposure rate and total inhaled dose. J. Appl. Physiol. 76: 2776-2784.

McDonnell, W. F.; Horstman, D. H.; Hazucha, M. J.; Seal, E., Jr.; Haak, E. D.; Salaam, S. A.; House, D. E. (1983) Pulmonary effects of ozone exposure during exercise: dose-response characteristics. J. Appl. Physiol.: Respir. Environ. Exercise Physiol. 54: 1345-1352.

McDonnell, W. F., III; Chapman, R. S.; Leigh, M. W.; Strope, G. L.; Collier, A. M. (1985) Respiratory responses of vigorously exercising children to 0.12 ppm ozone exposure. Am. Rev. Respir. Dis. 132: 875-879.

McDonnell, W. F.; Muller, K. E.; Bromberg, P. A.; Shy, C. M. (1993) Predictors of individual differences in acute response to ozone exposure. Am. Rev. Respir. Dis. 147: 818-825.

McDonnell, W. F.; Andreoni, S.; Smith, M. V. (1995) Proportion of moderately exercising individuals responding to low-level, multi-hour ozone exposure. Am. J. Respir. Crit. Care Med. 152: 589-596.

National Institutes of Health. (1991) Guidelines for the diagnosis and management of asthma. Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute, National Asthma Education Program; publication no. 91-3042.

Rombout, P. J. A.; Van Bree, L.; Heisterkamp, S. H.; Marra, M. (1989) The need for an eight hour ozone standard. In: Schneider, T.; Lee, S. D.; Wolters, G. J. R.; Grant, L. D., eds. Atmospheric ozone research and its policy implications: proceedings of the 3rd US-Dutch international symposium; May 1988; Nijmegen, The Netherlands. Amsterdam, The Netherlands: Elsevier Science Publishers; pp. 701-710. (Studies in environmental science 35).

Schwartz, J.; Gold, D.; Dockery, D. W.; Weiss, S. T.; Speizer, F. E. (1990) Predictors of asthma and persistent wheeze in a national sample of children in the United States: association with social class, perinatal events, and race. Am. Rev. Respir. Dis. 142: 555-562.

Seal, E., Jr.; McDonnell, W. F.; House, D. E.; Salaam, S. A.; Dewitt, P. J.; Butler, S. O.; Green, J.; Raggio, L.(1993) The pulmonary response of white and black adults to six concentrations of ozone. Am. Rev. Respir. Dis. 147: 804-810.

Sly, M. D. (1988) Mortality from asthma in children 1979-1984. Ann. Allergy 60: 433-443.

Smith, D. L.; Deshazo, R. D. (1993) Bronchoalveolar lavage in asthma: an update and perspective. Am. Rev. Respir. Dis. 148: 523-532.

Spektor, D. M.; Lippmann, M.; Lioy, P. J.; Thurston, G. D.; Citak, K.; James, D. J.; Bock, N.; Speizer, F. E.; Hayes, C. (1988) Effects of ambient ozone on respiratory function in active, normal children. Am. Rev. Respir. Dis. 137: 313-320.

Stanley, M. W. (1991) Diagnosis of pulmonary infections. In: Stanley, M. W.; Henry-Stanley, M. J.; Iber, C. Bronchoalveolar lavage: cytology and clinical applications. New York, NY: Igaku-Shoin; pp. 65-111.

Tepper, J. S.; Costa, D. L.; Doerfler, D.; Lehmann, J. R.; Stevens, M. A.; Madden, M. C. (1994) The relative contribution of concentration and duration to ozone (O3)-induced lung injury. Fundam. Appl. Toxicol.: submitted.

Thurston, G.D.; Ito, K.; Hayes, C.G.; Bates, D.V.; Lippmann, M. (1994) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ. Res. 65: 271-290.

U.S. Environmental Protection Agency. (1978) Air quality criteria for ozone and other photochemical oxidants. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-78-004. Available from: NTIS, Springfield, VA; PB80-124753.

U.S. Environmental Protection Agency. (1986) Air quality criteria for ozone and other photochemical oxidants. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report nos. EPA-600/8-84-020aF-eF. 5v. Available from: NTIS, Springfield, VA; PB87-142949.

U.S. Environmental Protection Agency. (1989) Review of the national ambient air quality standards for ozone: assessment of scientific and technical information. OAQPS staff paper. Research Triangle Park, NC: Office of Air Quality Planning and Standards; EPA report no. EPA-450/2-92/001. Available from: NTIS, Springfield, VA; PB92-190446.

Weiss, K. B.; Wagener, D. K. (1990) Changing patterns of asthma mortality: identifying target populations at high risk. JAMA J. Am. Med. Assoc. 264: 1683-1687.